10/ 726,486

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	SEP 09	ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS 4	OCT 03	MATHDI removed from STN
NEWS 5	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
NEWS 6	OCT 13	New CAS Information Use Policies Effective October 17, 2005
NEWS 7	OCT 17	STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools
NEWS 8	OCT 27	Free KWIC format extended in full-text databases
NEWS 9	OCT 27	DIOGENES content streamlined
NEWS 10	OCT 27	EPFULL enhanced with additional content
NEWS 11	NOV 14	CA/CAplus - Expanded coverage of German academic research
NEWS 12	NOV 30	REGISTRY/ZREGISTRY on STN(R) enhanced with experimental spectral property data

NEWS EXPRESS NOVEMBER 18 CURRENT VERSION FOR WINDOWS IS V8.01,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005.
V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
http://download.cas.org/express/v8.0-Discover/

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:21:21 ON 01 DEC 2005

=> file reg
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

10/ 726,486

FULL ESTIMATED COST 0.21 0.21

FILE 'REGISTRY' ENTERED AT 10:21:47 ON 01 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 29 NOV 2005 HIGHEST RN 868943-57-1
DICTIONARY FILE UPDATES: 29 NOV 2005 HIGHEST RN 868943-57-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

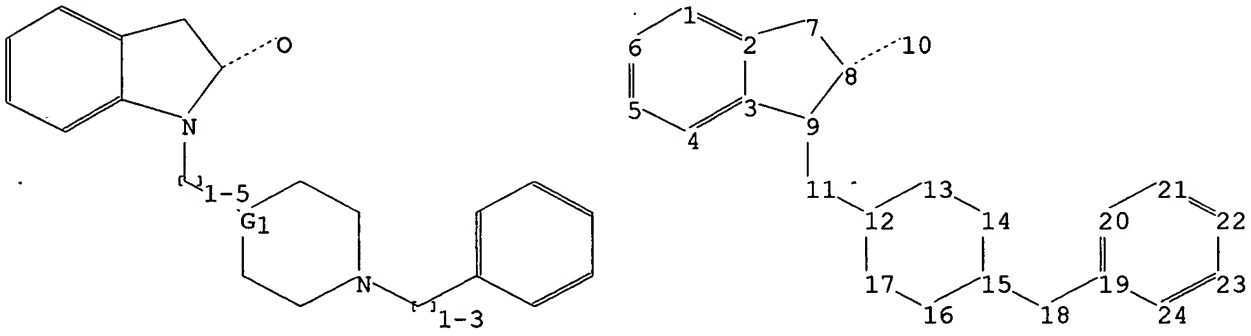
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10726488a.str



chain nodes :
10 11 18
ring nodes :
1 2 3 4 5 6 7 8 9 12 13 14 15 16 17 19 20 21 22 23 24
chain bonds :
8-10 9-11 11-12 15-18 18-19

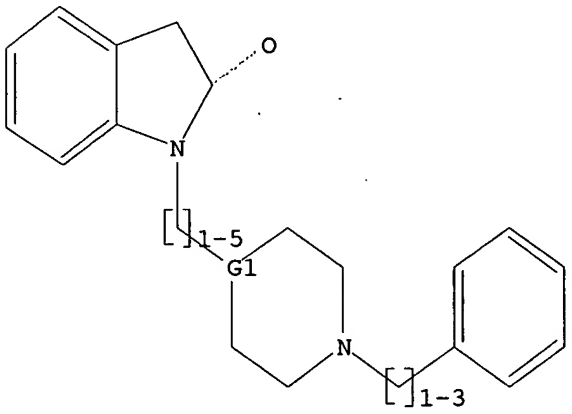
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-9 4-5 5-6 7-8 8-9 12-13 12-17 13-14 14-15 15-16
16-17 19-20 19-24 20-21 21-22 22-23 23-24
exact/norm bonds :
2-7 7-8 8-10 9-11 11-12 15-18 18-19
exact bonds :
3-9 8-9 12-13 12-17 13-14 14-15 15-16 16-17
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 19-20 19-24 20-21 21-22 22-23 23-24
isolated ring systems :
containing 1 : 12 : 19 :

G1:C,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS
11:CLASS 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:Atom

L1 STRUCTURE UPLOADED

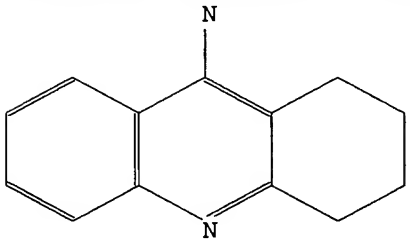
=> d l1
L1 HAS NO ANSWERS
L1 STR

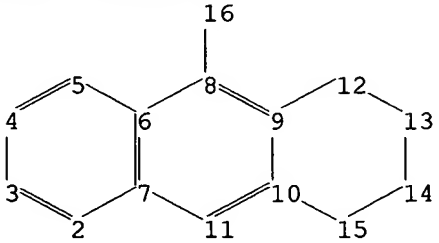


G1 C,N

Structure attributes must be viewed using STN Express query preparation.

=>
Uploading C:\Program Files\Stnexp\Queries\10726488b.str





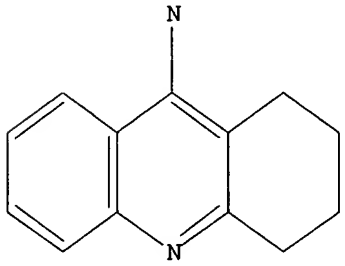
chain nodes :
16
ring nodes :
2 3 4 5 6 7 8 9 10 11 12 13 14 15
chain bonds :
8-16
ring bonds :
2-3 2-7 3-4 4-5 5-6 6-7 6-8 7-11 8-9 9-10 9-12 10-11 10-15 12-13
13-14 14-15
exact/norm bonds :
8-16
exact bonds :
9-12 10-15 12-13 13-14 14-15
normalized bonds :
2-3 2-7 3-4 4-5 5-6 6-7 6-8 7-11 8-9 9-10 10-11
isolated ring systems :
containing 2 :

G1:C,N

Match level :
2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS

L2 STRUCTURE UPLOADED

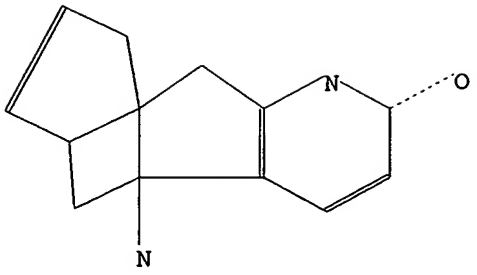
=> d l2
L2 HAS NO ANSWERS
L2 STR

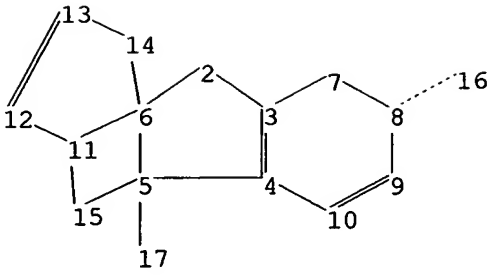


G1 C,N

Structure attributes must be viewed using STN Express query preparation.

=>
Uploading C:\Program Files\Stnexp\Queries\10726488c.str





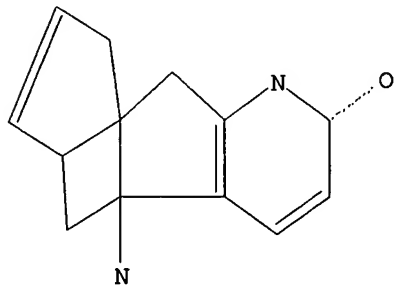
chain nodes :
16 17
ring nodes :
2 3 4 5 6 7 8 9 10 11 12 13 14 15
chain bonds :
5-17 8-16
ring bonds :
2-3 2-6 3-4 3-7 4-5 4-10 5-6 5-15 6-11 6-14 7-8 8-9 9-10 11-12 11-15
12-13 13-14
exact/norm bonds :
2-3 3-4 4-5 4-10 5-17 7-8 8-9 8-16 9-10 11-12 12-13 13-14
exact bonds :
2-6 3-7 5-6 5-15 6-11 6-14 11-15
isolated ring systems :
containing 2 :

G1:C,N

Match level :
2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS

L3 STRUCTURE UPLOADED

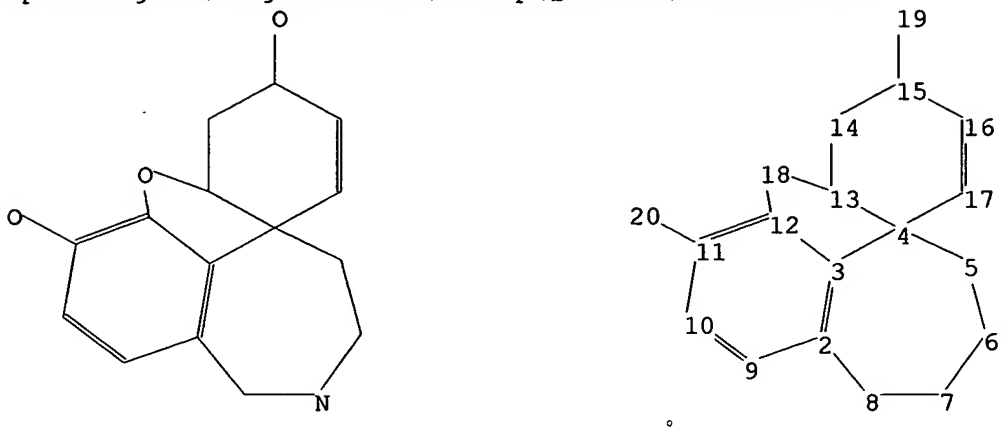
=> d l3
L3 HAS NO ANSWERS
L3 STR



G1 C,N

Structure attributes must be viewed using STN Express query preparation.

=>
Uploading C:\Program Files\Stnexp\Queries\10726488d.str



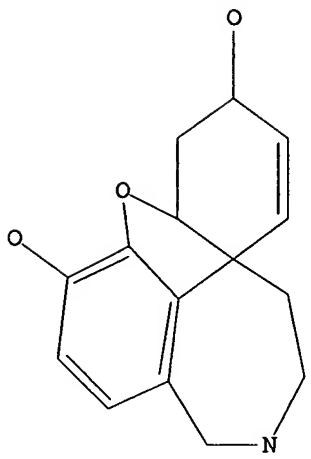
chain nodes :
19 20
ring nodes :
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
chain bonds :
11-20 15-19
ring bonds :
2-3 2-8 2-9 3-4 3-12 4-5 4-13 4-17 5-6 6-7 7-8 9-10 10-11 11-12 12-18
13-14 13-18 14-15 15-16 16-17
exact/norm bonds :
3-4 4-17 11-20 15-16 15-19 16-17
exact bonds :
2-8 4-5 4-13 5-6 6-7 7-8 12-18 13-14 13-18 14-15
normalized bonds :
2-3 2-9 3-12 9-10 10-11 11-12
isolated ring systems :
containing 2 :

G1:C,N

Match level :
2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:CLASS 20:CLASS

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR



G1 C,N

Structure attributes must be viewed using STN Express query preparation.

```
=> s l1 full
FULL SEARCH INITIATED 10:23:15 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     2535 TO ITERATE

100.0% PROCESSED     2535 ITERATIONS                          309 ANSWERS
SEARCH TIME: 00.00.01

L5          309 SEA SSS FUL L1

=> s l2 full
FULL SEARCH INITIATED 10:23:23 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     3015 TO ITERATE

100.0% PROCESSED     3015 ITERATIONS                         1662 ANSWERS
SEARCH TIME: 00.00.01

L6         1662 SEA SSS FUL L2

=> s l3 full
FULL SEARCH INITIATED 10:23:28 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -        2 TO ITERATE

100.0% PROCESSED        2 ITERATIONS                            0 ANSWERS
SEARCH TIME: 00.00.01

L7            0 SEA SSS FUL L3

=> s l4 full
FULL SEARCH INITIATED 10:23:34 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     1157 TO ITERATE

100.0% PROCESSED     1157 ITERATIONS                          783 ANSWERS
SEARCH TIME: 00.00.01

L8          783 SEA SSS FUL L4

=> file hcaplus
```

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	644.89	645.10

FILE 'HCAPLUS' ENTERED AT 10:23:44 ON 01 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Dec 2005 VOL 143 ISS 23
FILE LAST UPDATED: 30 Nov 2005 (20051130/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> d his

     (FILE 'HOME' ENTERED AT 10:21:21 ON 01 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 10:21:47 ON 01 DEC 2005
L1              STRUCTURE UPLOADED
L2              STRUCTURE UPLOADED
L3              STRUCTURE UPLOADED
L4              STRUCTURE UPLOADED
L5          309 S L1 FULL
L6         1662 S L2 FULL
L7            0 S L3 FULL
L8          783 S L4 FULL

     FILE 'HCAPLUS' ENTERED AT 10:23:44 ON 01 DEC 2005

=> s l5 or l6 or l7 or l8
           14 L5
         1511 L6
            0 L7
         1138 L8
L9       2515 L5 OR L6 OR L7 OR L8

=> remove dup 19
DUP IS NOT VALID HERE
The DELETE command is used to remove various items stored by the
system.

To delete a saved query, saved answer set, saved L-number list, SDI
request, batch request, mailing list, or user-defined cluster, format,
or search field, enter the name.  The name may include ?  for left,
right, or simultaneous left and right truncation.
```

Examples:

```
  DELETE BIO?/Q           - delete query names starting with BIO
  DELETE ?DRUG/A          - delete answer set names ending with DRUG
  DELETE ?ELEC?/L         - delete L-number lists containing ELEC
  DELETE ANTICOAG/S       - delete SDI request
  DELETE ENZYME/B         - delete batch request
  DELETE .MYCLUSTER       - delete user-defined cluster
  DELETE .MYFORMAT        - delete user-defined display format
  DELETE .MYFIELD         - delete user-defined search field
  DELETE NAMELIST MYLIST - delete mailing list
```

To delete an ordered document or an offline print, enter its number.

Examples:

```
  DELETE P123001C         - delete print request
  DELETE D134002C         - delete document order request
```

To delete an individual L-number or range of L-numbers, enter the L-number or L-number range. You may also enter DELETE LAST followed by a number, n, to delete the last n L-numbers. RENUMBER or NORENUMBER may also be explicitly specified to override the value of SET RENUMBER.

Examples:

```
  DELETE L21              - delete a single L-number
  DELETE L3-L6            - delete a range of L-numbers
  DELETE LAST 4           - delete the last 4 L-numbers
  DELETE L33-             - delete L33 and any higher L-number
  DELETE -L55             - delete L55 and any lower L-number
  DELETE L2-L6 RENUMBER - delete a range of L-numbers and
                            renumber remaining L-numbers
  DELETE RENUMBER         - renumber L-numbers after deletion of
                            intermediate L-numbers
```

Entire sets of saved items, SDI requests, batch requests, user-defined items, or E-numbers can be deleted.

Examples:

```
  DELETE SAVED/Q - delete all saved queries
  DELETE SAVED/A - delete all saved answer sets
  DELETE SAVED/L - delete all saved L-number lists
  DELETE SAVED   - delete all saved queries, answer sets,
                   and L-number lists
  DELETE SAVED/S - delete all SDI requests
  DELETE SAVED/B - delete all batch requests
  DELETE CLUSTER - delete all user-defined clusters
  DELETE FORMAT  - delete all user-defined display formats
  DELETE FIELD   - delete all user-defined search fields
  DELETE SELECT  - delete all E-numbers
  DELETE HISTORY - delete all L-numbers and restart the
                   session at L1
```

To delete an entire multifile SDI request, enter DELETE and the name of the request. To delete a component from the multifile SDI, enter DELETE and the name of the component.

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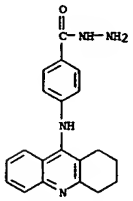
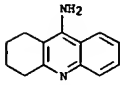
```
=> .
. IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

     (FILE 'HOME' ENTERED AT 10:21:21 ON 01 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 10:21:47 ON 01 DEC 2005
L1                STRUCTURE UPLOADED
L2                STRUCTURE UPLOADED
L3                STRUCTURE UPLOADED
L4                STRUCTURE UPLOADED
L5             309 S L1 FULL
L6            1662 S L2 FULL
L7               0 S L3 FULL
L8             783 S L4 FULL

     FILE 'HCAPLUS' ENTERED AT 10:23:44 ON 01 DEC 2005
L9            2515 S L5 OR L6 OR L7 OR L8

=> s l9 and (acetylcholine or muscarinic or urina? or bladder or dysuria)
           72727 ACETYLCHOLINE
           24508 MUSCARINIC
          124267 URINA?
           32086 BLADDER
             227 DYSURIA
L10           486 L9 AND (ACETYLCHOLINE OR MUSCARINIC OR URINA? OR BLADDER OR
                  DYSURIA)

=> s l10 not py>1999
         6126486 PY>1999
L11           284 L10 NOT PY>1999

=> d l11 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 284 ANSWERS - CONTINUE? Y/(N):y
```

L11 ANSWER 1 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:880424 HCAPLUS
DOCUMENT NUMBER: 134:252314
TITLE: New 9-(para-substituted anilino)tetrahydroacridines as acetylcholinesterase inhibitors
AUTHOR(S): Ebied, M. Y.; Kamel, M. M.; Ragab, F.; Nofal, Z. M.; Ahmed, A. A. E.; Zaghary, W. A.; El-Kady, M.
CORPORATE SOURCE: Faculty of Pharmacy, Cairo University, Egypt
SOURCE: Al-Azhar Journal of Pharmaceutical Sciences (1999), 24, 114-132
CODEN: AAJPFT; ISSN: 1110-1644
PUBLISHER: Al-Azhar University, Faculty of Pharmacy
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:252314
AB Some new title compds. are prepared 9-(P-acetylanilino)-1,2,3,4-tetrahydroacridine, Et p-[1,2,3,4-tetrahydroacridin-9-yl]aminobenzoate and its acid hydrazide, 9-(4-aminophenoxy)-1,2,3,4-tetrahydroacridine, a 9-[A2-pyrazolin-3-yl]anilinotetrahydroacridine derivative, 1-[4-(1,2,3,4-tetrahydroacridin-9-yl) aminobenzoyl]-4-phenylsemicarbazide, and 9-[p-(3,5-dimethylpyrazol-2-yl)carbonylanilino]-1,2,3,4-tetrahydroacridine showed considerable acetylcholinesterase inhibitory activity as indicated by potentiation of acetylcholine induced contraction of isolated frog rectus abdominus.
IT 331670-68-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(new 9-(para-substituted anilino)tetrahydroacridines as acetylcholinesterase inhibitors)
RN 331670-68-9 HCAPLUS
CN Benzoic acid, 4-[(1,2,3,4-tetrahydro-9-acridinyl)amino]-, hydrazide (9CI) (CA INDEX NAME)



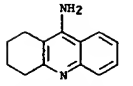
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:264781 HCAPLUS
DOCUMENT NUMBER: 133:318417
TITLE: A new view on the mechanism of action of reversible cholinesterase inhibitors as drugs for prophylaxis
AUTHOR(S): Tonkopii, V. D.
CORPORATE SOURCE: Institute of Limnology, Russian Academy of Sciences, St. Petersburg, 196199, Russia
SOURCE: NATO Science Series, 1: Disarmament Technologies (1999), 25(NBC Risks: Current Capabilities and Future Perspectives for Protection), 161-163
CODEN: NSDTF8; ISSN: 1389-1820
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was conducted to examine the efficiency of various cholinesterase reversible inhibitors (RIs) in order to elucidate further on the mechanism of RI protective action against organophosphate (OP) poisoning. The following RIs were used: galanthamine (alkaloid from the Caucasian snowdrop Galanthus woronovi), tacrine, bis-quaternary compound ambenonium and some carbamates (physostigmine, aminostigmine and pyridostigmine). The kinetics of the inhibition of the purified human erythrocyte acetylcholinesterase (AChE) by different RIs were studied. Results indicated that the protective action of RIs against OP poisonings depends primarily on the ability of the RI to inhibit brain AChE, forming a semistable complex of RI-enzyme which can spontaneously breakdown to liberate the enzyme. The mode of connection of RI with AChE and the sensitivity of the complex of RI-enzyme to acetylcholine are also important. The preference of competitive RI types of galanthamine and carbamates for prophylaxis against OP poisonings was demonstrated.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(mechanism of action of reversible cholinesterase inhibitors as drugs for prophylaxis of organophosphate poisoning)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



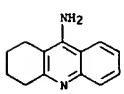
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:40254 HCAPLUS
DOCUMENT NUMBER: 132:317889
TITLE: Synergistic effects of tetrahydroaminoacridine and lithium on cholinergic function after excitotoxic basal forebrain lesions in rat
AUTHOR(S): Arendt, T.; Lehmann, K.; Seeger, G.; Gartner, U.
CORPORATE SOURCE: Department of Neuroanatomy, Paul Flechsig Institute of Brain Research, University of Leipzig, Germany
SOURCE: Pharmacopsychiatry (1999), 32(6), 242-247
CODEN: PHRMEZ; ISSN: 0176-3679
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of lithium and tetrahydroaminoacridine (THA), either alone or in combination, were tested in an animal model of excitotoxic cholinergic deafferentation of the cerebral cortex. Rats received ibotenic acid lesions of cholinergic basal forebrain nuclei resulting in a 30% to 40% depletion of both cortical choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity. Lithium as well as THA, given sep. either prior or subsequently to the development of the lesion, had small but significant effects on the recovery of cortical ChAT and AChE activity. Applied in combination, these drugs clearly showed synergistic effects. These potentiating actions might be due to neuroprotective/neurotrophic mechanisms as well as to effects on acetylcholine turnover and muscarinic receptor-coupled phosphoinositide turnover. Similar approaches of combination therapy might prove useful for the management of mental disorders associated with cholinergic dysfunction.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic effects of tetrahydroaminoacridine and lithium on cholinergic function after excitotoxic basal forebrain lesions in rat)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:790834 HCAPLUS
DOCUMENT NUMBER: 132:231473
TITLE: Tacrine is not an ideal probe drug for measuring CYP1A2 activity in vivo
AUTHOR(S): Larsen, J. T.; Hansen, L. L.; Brosen, K.
CORPORATE SOURCE: Institute of Public Health, University of Southern Denmark, Odense, DK-5000, Den.
SOURCE: British Journal of Clinical Pharmacology (1999), 48(5), 663-668
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aims The aim of the present study was to examine the CYP1A2 substrate tacrine as a possible alternative to caffeine for assessing CYP1A2 activity in vivo. Methods Eighteen, healthy, nonsmoking men participated. Each volunteer was tested by caffeine (200 mg orally), and caffeine metabolic ratios were calculated Subsequently, on two occasions, separated by at least 4 wk, each volunteer was tested with tacrine (40 mg orally). The apparent oral clearance, partial clearances and different metabolic ratios of tacrine were determined Results The median oral clearances of tacrine in the two study periods were 1893 l h-1 (range: 736-3098) and 1890 l h-1 (range: 438-4175), resp. The interindividual coefficient of variation was 42% and 49%, resp. The intraindividual coeffs. of variation ranged from 0.28% to 64% (median: 13%). In both study periods, the oral clearance of tacrine correlated with the caffeine urinary metabolic ratio. However, only modest magnitudes of correlation were observed (rs: 0.64-0.66, $P < 0.01$). No tacrine metabolic ratio correlating with the oral clearance of tacrine was found. Conclusion The applicability of tacrine as a probe drug for measuring CYP1A2 activity in vivo appears limited.
IT 321-64-2, Tacrine
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(tacrine as a probe drug for measuring human CYP1A2 activity in vivo)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

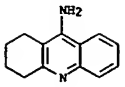
L11 ANSWER 5 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:693076 HCAPLUS
DOCUMENT NUMBER: 131:332022
TITLE: Effect of donepezil hydrochloride (E2020) on basal concentration of extracellular **acetylcholine** in the hippocampus of rats
AUTHOR(S): Kosasa, Takashi; Kuriya, Yuka; Matsui, Kenji; Yamanishi, Yoshiharu
CORPORATE SOURCE: Tsukuba Research Laboratories, Tsukuba, 300-2635, Japan
SOURCE: European Journal of Pharmacology (1999), 380(2/3), 101-107
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of oral centrally acting **acetylcholine** esterase (AChE) inhibitors donepezil HCl, tacrine HCl, and ENA-713 (rivastigmine hydrogentartrate) developed for the treatment of Alzheimer disease on the extracellular **acetylcholine** concns. in the brain hippocampus of rats were evaluated using microdialysis without adding cholinesterase inhibitors to the perfusion solution We also compared the inhibition of brain AChE and brain concns. of the 3 drugs. Donepezil at 2.5 mg/kg and tacrine at 5 mg/kg had significant effects for >6 h. At these doses, the maximum increases were 499 and 422% of the pretreatment levels and were observed at .apprx.1.5 and .apprx.2 h after administration of donepezil and tacrine, resp. ENA-713 had significant effects at 0.625, 1.25, and 2.5 mg/kg, which lasted for about 1, 2, and 4 h, resp. The maximum increases produced by these doses at .apprx.0.5 h after administration were 190, 346, and 458% of the pretreatment levels, resp. The time courses of brain AChE inhibition with 2.5 mg donepezil/kg, 10 mg tacrine/kg, and 2.5 mg ENA-713/kg were mirror images of the extracellular **acetylcholine** -increasing action at the same doses. The time courses of brain concns. of the drugs after oral administration of 2.5 mg donepezil/kg and 10 mg tacrine/kg were consistent with the course of brain AChE inhibition at the same doses; there was a linear relation between these parameters. Brain concns. of ENA-713 given at 2.5 mg/kg was below the limit of quantification at all time points measured. Thus, oral administration of donepezil, tacrine, and ENA-713 increases **acetylcholine** concns. in the synaptic cleft of the brain hippocampus mostly through AChE inhibition. Donepezil has a more potent activity than tacrine and a longer-lasting effect than ENA-713 on the central cholinergic system.

IT **1684-40-8**, Tacrine hydrochloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(donepezil HCl (E2020) effects on basal concns. of extracellular **acetylcholine** in brain hippocampus of rats)

RN 1684-40-8 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)

L11 ANSWER 5 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HCl

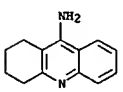
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:691805 HCAPLUS
DOCUMENT NUMBER: 132:30233
TITLE: Evaluation of the FLEXX incremental construction algorithm for protein-ligand docking
AUTHOR(S): Kramer, Bernd; Rarey, Matthias; Lengauer, Thomas
CORPORATE SOURCE: Institute for Algorithms and Scientific Computing (SCAI), German National Research Center for Information Technology (GMD), Sankt Augustin, Germany
SOURCE: Proteins: Structure, Function, and Genetics (1999), 37(2), 228-241
CODEN: PSFGEY; ISSN: 0887-3585
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report on a test of FLEXX, a fully automatic docking tool for flexible ligands, on a highly diverse data set of 200 protein-ligand complexes from the Protein Data Bank. In total 46.5% of the complexes of the data set can be reproduced by a FLEXX docking solution at rank 1 with an rms deviation (RMSD) from the observed structure of less than 2 Å. This rate rises to 70% if one looks at the entire generated solution set. FLEXX produces reliable results for ligands with up to 15 components which can be docked in 80% of the cases with acceptable accuracy. Ligands with more than 15 components tend to generate wrong solns. more often. The average runtime of FLEXX on this test set is 93 s per complex on a SUN Ultra-30 workstation. In addition, we report on "cross-docking" expts., in which several receptor structures of complexes with identical proteins have been used for docking all cocrystd. ligands of these complexes. In most cases, these expts. show that FLEXX can acceptably dock a ligand into a foreign receptor structure. Finally we report on screening runs of ligands out of a library with 556 entries against ten different proteins. In eight cases FLEXX is able to find the original inhibitor within the top 7% of the total library.

IT **321-64-2**, Tacrine
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(evaluation of FLEXX incremental construction algorithm for protein-ligand docking)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

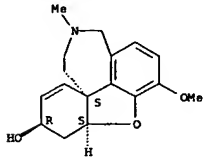
L11 ANSWER 7 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:574043 HCAPLUS
DOCUMENT NUMBER: 131:281884
TITLE: The role of **acetylcholine** in the pathogenesis of convulsive states of various etiology
AUTHOR(S): Kosmachev, A. B.; Mukovsky, L. A.; Kolgo-Saburov, E. B.; Khobotova, E. I.; Kubarskaya, L. G.
CORPORATE SOURCE: Lab. Biochemistry and Lab. Toxicology, Inst. Toxicology Russian Federation Ministry of Public Health, St. Petersubrg, 193019, Russia
SOURCE: Eksperimental'naya i Klinicheskaya Farmakologiya (1999), 62(2), 7-9
CODEN: EKFAE9; ISSN: 0869-2092
PUBLISHER: Izdatel'stvo Folium
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB Expts. were performed on rats to study the dynamics of changes in some parameters characterizing the state of the cholinergic part of the nervous system during the development of convulsions induced by various convulsants (anticholinesterases and GABA-lytics). Convulsants of different types increased the total concentration of **acetylcholine** and decreased the activity of acetylcholinesterase in the brain beginning at the first signs of intoxication. At the appearance of convulsions induced by these agents, the concns. of **muscarinic** receptor-bound **acetylcholine** increased. Thus, dependent on its concentration in the synaptic cleft, **acetylcholine** may contribute to the development of convulsions or to their arrest.

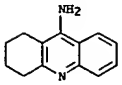
IT **357-70-0**, Galanthamine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**acetylcholine** role in the pathogenesis of convulsive states of various etiol.)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



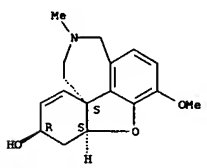
L11 ANSWER 8 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:476713 HCAPLUS
DOCUMENT NUMBER: 131:237860
TITLE: Combining tacrine with milameline reverses a scopolamine-induced impairment of continuous performance in rhesus monkeys
AUTHOR(S): Callahan, Michael J.
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Neuroscience Therapeutics, Division of Warner-Lambert Company, Ann Arbor, MI, 48105, USA
SOURCE: Psychopharmacology (Berlin) (1999), 144(3), 234-238
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cholinomimetic therapy in Alzheimer's disease (AD) has been hampered by narrow efficacious dose ranges and dose-limiting side effects. These limitations highlight the need for an alternative therapeutic approach for the symptomatic treatment of AD. To determine in rhesus monkeys if combined treatment with the acetylcholinesterase inhibitor tacrine (Cognex) and the muscarinic agonist milameline improve behavioral efficacy in a scopolamine-reversal task without potentiating adverse side effects. Behavioral performance of rhesus monkeys was measured using a continuous performance task. The effects of tacrine and milameline, sep. or in combination, were determined following administration of an impairing dose of the anticholinergic scopolamine. In addition, tacrine and milameline were given similarly in the absence of scopolamine to determine the presence of adverse side effects. Tacrine and milameline, sep. or in combination, reversed the scopolamine-induced decrease in responses on a continuous performance task. Administered in combination, tacrine and milameline significantly improved performance on this task at lower doses and across a broader dose range than when given sep. In the absence of scopolamine, combined treatment did not potentiate the appearance of side effects or produce adverse events significantly different from those observed with either compound alone. Tacrine and milameline given in combination broadened the range of doses significantly reversing a scopolamine-induced impairment without potentiating adverse side effects.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combining tacrine with milameline reverses a scopolamine-induced impairment of continuous performance in rhesus monkeys in relation to Alzheimer's disease treatment and adverse side effects)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 8 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

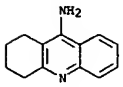
L11 ANSWER 9 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:434292 HCAPLUS
DOCUMENT NUMBER: 131:252411
TITLE: Effect of the acetylcholinesterase inhibitor galanthamine on learning and memory in prolonged alcohol intake rat model of acetylcholine deficit
AUTHOR(S): Iliev, A.; Traykov, V.; Prodanov, D.; Mantchev, G.; Yakimova, K.; Krushkov, I.; Boyadjieva, N.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Medical University, Sofia, Bulg.
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology (1999), 21(4), 297-301
CODEN: MFEPDX; ISSN: 0379-0355
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study examined the effect of the acetylcholinesterase inhibitor galanthamine in male Wistar rats receiving prolonged alc. intake, as a model of acetylcholine deficit. After 16 wk of alc. intake and a 2-wk pause, rats administered galanthamine (2.5 mg/kg/day i.p.) showed an improved speed of learning and short-term memory in the shuttle box test as compared to the saline-injected alc. group. Four weeks later, significant improvement of the passive avoidance memory in alc. galanthamine-treated rats was noted in the 8-arm radial maze (14-day test duration) as compared to the saline-injected alc. group. During the 1st week in the shuttle box test, nonalcoholic galanthamine-treated animals exhibited impaired performance as compared to the untreated nonalcoholic control, while 4 wk later, in the 8-arm radial maze, there was no difference between the groups. The results show that galanthamine improves the speed of learning, short-term memory and spatial orientation of rats in conditions of prolonged alc. intake.
IT 357-70-0, Galanthamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acetylcholinesterase inhibitor galanthamine effect on learning and memory in alc.-induced acetylcholine deficit)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



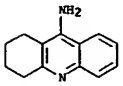
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:433714 HCAPLUS
DOCUMENT NUMBER: 131:196296
TITLE: Comparative model building of human butyrylcholinesterase
AUTHOR(S): Ekholm, Michaela; Konschin, Henrik
CORPORATE SOURCE: Department of Chemistry, University of Helsinki, Helsinki, FIN-00014, Finland
SOURCE: THEOCHEM (1999), 467(2), 161-172
CODEN: THEODJ; ISSN: 0166-1280
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A model of the human butyrylcholinesterase was constructed on the basis of the structure of acetylcholinesterase from Torpedo californica, using comparative modeling. The program MODELLER was also used to develop a model of the protein. The active site, consisting of the catalytic triad, a choline binding locus, an oxyanion hole and an acyl binding pocket were investigated by superimposing different substrates and inhibitors in the active site. The structures were relaxed using mol. mechanics calcns. Van der Waals vols. of different substrates and inhibitors at the active site were also investigated. The interaction between ligands and various residues is discussed.
IT 321-64-2, Tacrine
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(comparative model building of human butyrylcholinesterase)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



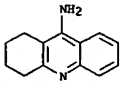
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:403135 HCAPLUS
DOCUMENT NUMBER: 131:208484
TITLE: Cholinergic therapies in Alzheimer's disease
AUTHOR(S): Siddiqui, Muhammad F.; Levey, Allan I.
CORPORATE SOURCE: Department of Neurology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Drugs of the Future (1999), 24(4), 417-424
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 81 refs., on the cholinergic therapies in Alzheimer's disease.
IT 321-64-2, Tacrine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cholinergic therapies in Alzheimer's disease)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



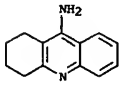
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:321084 HCAPLUS
DOCUMENT NUMBER: 131:111317
TITLE: Divided attention-enhancing effects of AF102B and THA in aging monkeys
AUTHOR(S): O'Neill, J.; Fitten, L. J.; Siembieda, D. W.; Crawford, K. C.; Halgren, E.; Fisher, A.; Refai, D.
CORPORATE SOURCE: Brain Research Institute and Department of Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, 90024, USA
SOURCE: Psychopharmacology (Berlin) (1999), 143(2), 123-130
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypothesis that cholinergic drugs improve spatial divided attention in primates was tested via a computer task requiring simultaneous tracking of 2 visual targets in 3 young and 2 aged healthy bonnet macaques. Task accuracy (number of correct responses) and reaction time (RT) were measured 2 h after administration of either the M1 agonist ±-cis-2-methylspiro-(1,3-oxathiolane-5,3')quinuclidine (AF102B; 0.1-2.1 mg/kg, i.m.) or the cholinesterase inhibitor 9-amino-1,2,3,4-tetrahydroaminoacridine (THA; 0.5-2.0 mg/kg orally). Accuracy increased for four of the 5 monkeys at appropriate doses of one or both cholinomimetics, accompanied in 2 monkeys by a drop in RT. Responses were less uniform to THA than to AF102B. For the 5-monkey group at best dose, accuracy increased 34% (THA) or 43% (AF102B) above basal values with no significant change in RT and with minimal untoward effects. Cholinotherapy may improve divided attention in young and aged healthy primates.
IT 321-64-2, THA
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(divided attention-enhancing effects of AF102B and aminotetrahydroaminoacridine in aging monkeys)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

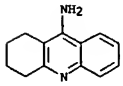


REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:260670 HCAPLUS
DOCUMENT NUMBER: 130:305938
TITLE: Pharmacologic treatment of Alzheimer's disease
AUTHOR(S): Tohgi, Hideo; Takahashi, Satoshi
CORPORATE SOURCE: Dep. Neurol., Iwate Med. Univ., Morioka, 020-8505, Japan
SOURCE: No no Kagaku (1999), 21(4), 459-463
CODEN: NNOKFZ; ISSN: 1343-4144
PUBLISHER: Seiwa Shoten
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 31 refs., on effects of acetylcholine esterase inhibitors (tacrine, donepezil, and metrifonate), estrogen replacement therapy, antioxidants, and nonsteroidal anti-inflammatory drugs on cognitive deficits of Alzheimer's disease.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. treatment of Alzheimer's disease)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 14 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:236012 HCAPLUS
DOCUMENT NUMBER: 131:100507
TITLE: Reappraising neurotransmitter-based strategies
AUTHOR(S): Moller, Hans-Jurgen
CORPORATE SOURCE: Psychiatric Hospital of the Ludwig-Maximilian-University, Munich, 80336, Germany
SOURCE: European Neuropsychopharmacology (1999), 9(Suppl. 2), S53-S59
CODEN: EURNE8; ISSN: 0924-977X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 56 refs. A number of observations support the hypothesis that a central deficit in acetylcholine (ACh) may be responsible for the initiation of Alzheimer's disease (AD). For example, cholinergic innervation in AD is reduced in areas of the brain important for processing information. Further, reduced concns. of choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of ACh, correlate with the number of β-amyloid senile plaques and cognitive dysfunction in AD patients. Consequently, several strategies to increase cholinergic neurotransmission have been developed, including ACh precursors, ACh release enhancers, cholinesterase (ChE) inhibitors, and receptor agonists. Although ChE inhibitors appear to be the most promising, tacrine, the first ChE inhibitor to be registered and approved for the treatment of AD, has significant tolerability problems. Thus, ChE inhibitors with improved side-effect profiles have been developed and subsequently awarded marketing approval. However, in addition to the cholinergic system that is the most severely affected neurotransmitter system in AD, other neurotransmitter systems may be involved (serotonergic, noradrenergic, and glutamatergic). Therefore, bifunctional compds. or combinations of drugs may provide addnl. therapeutic value.
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reappraising neurotransmitter-based strategies for Alzheimer's disease in humans)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

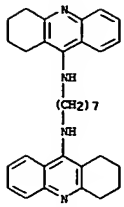
L11 ANSWER 15 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:188030 HCAPLUS
DOCUMENT NUMBER: 131:593
TITLE: Attenuation of scopolamine-induced deficits in navigational memory performance in rats by bis(7)-tacrine, a novel dimeric AChE inhibitor
AUTHOR(S): Wang, Hong; Carlier, Paul R.; Ho, Wing-Lok; Lee, Nelson Tze-Kin; Pang, Yuan-Ping; Han, Yi-Fan
CORPORATE SOURCE: Department of Biochemistry, Hong Kong University of Science and Technology, Hongkong, Peop. Rep. China
SOURCE: Zhongguo Yaoli Xuebao (1999), 20(3), 211-217
CODEN: CYLPDN; ISSN: 0253-9756
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the effects of 1,7-N-heptylene-bis-9,9'-amino-1,2,3,4-tetrahydroacridine [bis (7)-tacrine], a novel dimeric acetylcholine-sterase inhibitor (AChEI) derived from 9-amino-1,2,3,4-tetrahydroaminoacridine (tacrine), on scopolamine-induced spatial memory impairment. The effects of bis(7)-tacrine were investigated on the 5-d performance of young adult rats in the Morris water maze. The latency to find the platform in the water maze was measured to evaluate performance. Tacrine was used as a reference drug. Scopolamine (0.3 mg·kg-1, i.p.) resulted in an increase in latency period (> 100 % increase) as compared with saline treated controls. Both bis (7)-tacrine and tacrine lessened the increased latency induced by scopolamine to the level of saline control group. The relative potency of bis (7)-tacrine (0.35 μmol·kg-1, ig or i.p.) to shorten the escape latency was 24 or 12 times of tacrine (8.52 μmol·kg-1 ig, 4.26 μmol·kg-1 i.p.) following ig or i.p. administration, resp. There appeared to be an inverse bell-shape dose-dependent effect for both compds. tested. Bis (7)-tacrine is a more potent and orally active AChEI than tacrine, and has potential for the palliative treatment of Alzheimer disease.

IT 181865-13-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(attenuation of scopolamine-induced deficits in navigational memory performance by the acetylcholine-sterase inhibitor bis(7)-tacrine)

RN 181865-13-4 HCAPLUS
CN 1,7-Heptanediamine, N,N'-bis(1,2,3,4-tetrahydro-9-acridinyl)- (9CI) (CA INDEX NAME)

L11 ANSWER 15 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



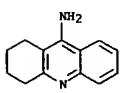
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:159251 HCAPLUS
DOCUMENT NUMBER: 130:332723
TITLE: A comparative study in rats of the in vitro and in vivo pharmacology of the acetylcholinesterase inhibitors tacrine, donepezil and NXX-066
AUTHOR(S): Snape, M. F.; Misra, A.; Murray, T. K.; De Souza, R. J.; Williams, J. L.; Cross, A. J.; Green, A. R.
CORPORATE SOURCE: Astra Neuroscience Research Unit, London, WC1N 1PJ, UK
SOURCE: Neuropharmacology (1999), 38(1), 181-193
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro and in vivo effects of the novel acetylcholinesterase inhibitors donepezil and NXX-066 have been compared to tacrine. Using purified acetylcholinesterase from elec. eel both tacrine and donepezil were shown to be reversible mixed type inhibitors, binding to a similar site on the enzyme. In contrast, NXX-066 was an irreversible non-competitive inhibitor. All three compds. were potent inhibitors of rat brain acetylcholinesterase (IC50 [nM]; tacrine: 125; NXX-066: 148; donepezil: 33). Tacrine was also a potent butyrylcholinesterase inhibitor. Donepezil and tacrine displaced [3H]pirenzepine binding in rat brain homogenates (IC50 values [μM]; tacrine: 0.7; donepezil: 0.5) but NXX-066 was around 80 times less potent at this M1-muscarinic site. Studies of carbachol stimulated increases in [Ca2+]i in neuroblastoma cells demonstrated that both donepezil and tacrine were M1 antagonists. Ligand binding suggested little activity of likely pharmacol. significance with any of the drugs at other neurotransmitter sites. I.p. administration of the compds. to rats produced dose dependent increases in salivation and tremor (ED50 [μmol/kg]; tacrine: 15, NXX-066: 35, donepezil: 6) with NXX-066 having the most sustained effect on tremor. Following oral administration, NXX-066 had the slowest onset but the greatest duration of action. The relative potency also changed, tacrine having low potency (ED50 [μmol/kg]; tacrine: 200, NXX-066: 30, donepezil: 50). Salivation was severe only in tacrine treated animals. Using in vivo microdialysis in cerebral cortex, both NXX-066 and tacrine were found to produce a marked (at least 30-fold) increase in extracellular acetylcholine which remained elevated for more than 2 h after tacrine and 4 h after NXX-066. The results are discussed in relation to the treatment of Alzheimer's disease with acetylcholinesterase inhibitors.

IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparative study in rats of in vitro and in vivo pharmacol. of acetylcholinesterase inhibitors tacrine and donepezil and NXX-066 in relation to Alzheimer's disease treatment)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



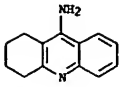
L11 ANSWER 16 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:140303 HCAPLUS
DOCUMENT NUMBER: 130:291945
TITLE: The role of ventrolateral striatal acetylcholine in the production of tacrine-induced jaw movements
AUTHOR(S): Cousins, Michael S.; Finn, Marianne; Trevitt, Jennifer; Carriero, Debbie L.; Conlan, Aimee; Salamone, John D.
CORPORATE SOURCE: Department of Psychology, University of Connecticut, Storrs, CT, 06269-1020, USA
SOURCE: Pharmacology, Biochemistry and Behavior (1999), 62(3), 439-447
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The anticholinesterase tacrine induces tremulous jaw movements in rats, and considerable evidence indicates that this response is dependent upon ventrolateral striatal mechanisms. Three expts. were conducted to study the relation between ventrolateral striatal acetylcholine and the production of tremulous jaw movements. In Experiment 1, intracranial microinjection of the acetylcholine synthesis inhibitor hemicholinium-3 into the ventrolateral neostriatum reduced tremulous jaw movements induced by 5.0 mg/kg tacrine. Microinjection of hemicholinium into a cortical site dorsal to striatum (Experiment 2) was without significant effect upon tacrine-induced tremulous jaw movements. In Experiment 3, rats were implanted with dialysis probes in the ventrolateral striatum to measure extracellular levels of acetylcholine during tacrine-induced jaw movements. Tacrine (2.5-5.0 mg/kg) increased both extracellular acetylcholine and tremulous jaw movements. The 5.0 mg/kg dose of tacrine produced a substantial increase in ventrolateral striatal acetylcholine levels (324% of baseline within 30 min). Across all tacrine-treated rats there was a significant linear correlation between tremulous jaw movements and acetylcholine levels during the first 30-min postinjection period. This correlation was largely due to the group that received 5.0 mg/kg tacrine; within this group, there was a very high correlation between tremulous jaw movements and acetylcholine levels in the first sample after injection. These data are consistent with the notion that tremulous jaw movements induced by tacrine are mediated by ventrolateral striatal acetylcholine. Moreover, these results suggest that dialysis methods could be used to monitor the relation between striatal acetylcholine and tremulous movements induced by a variety of different conditions.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ventrolateral striatal acetylcholine role in production of tacrine-induced jaw movements)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 17 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

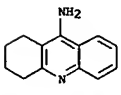


REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:118107 HCAPLUS
DOCUMENT NUMBER: 130:347244
TITLE: Reduction of motoric agitation and restlessness by AF102B and tacrine in the macaque
AUTHOR(S): Fitten, L. Jaime; Ortiz, Freddy; Siembieda, Douglas W.; O'Neill, Joseph; Halgren, Eric; Fisher, Abraham
CORPORATE SOURCE: U.S. Department of Veterans Affairs Sepulveda Medical Centers, Los Angeles, CA, USA
SOURCE: Journal of Neuropsychiatry and Clinical Neurosciences (1999), 11(1), 79-85
CODEN: JNCNE7; ISSN: 0895-0172
PUBLISHER: American Psychiatric Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cholinesterase inhibitor tacrine (THA) and the M1 muscarinic agonist AF102B (cevimeline), both reported to enhance cognition in animals and humans, were tested in macaques for reduction of spontaneous, random movements. The monkeys were given low- and high-dose AF102B i.m., and low- and high-dose THA orally. The high doses of both THA and AF102B reduced movements without overt side effects, warranting further research on the agitation-reducing potential of cognition-enhancing cholinomimetic drugs.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(reduction of motor agitation and restlessness by the cholinergic drugs AF102B and tacrine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

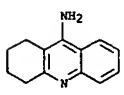


REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:20777 HCAPLUS
DOCUMENT NUMBER: 130:191818
TITLE: Oxotremorine suppresses thalamocortical oscillations via thalamic muscarinic acetylcholine receptors
AUTHOR(S): Puolivali, J.; Jakala, P.; Koivisto, E.; Riekkinen, P., Jr.
CORPORATE SOURCE: Department of Neuroscience and Neurology, University of Kuopio and Kuopio University Hospital, Kuopio, FIN-70211, Finland
SOURCE: Psychopharmacology (Berlin) (1998), 140(3), 285-292
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated whether the local intrathalamic infusion of a muscarinic acetylcholine receptor agonist (oxotremorine) at either the reticular nucleus of thalamus (NRT) or the ventroposteromedial nucleus of thalamus (VPM) suppresses thalamocortically generated neocortical high-voltage spindles (HVSs). In addition, we studied whether the intracerebroventricular (ICV) infusion of a selective muscarinic M2 acetyl-choline receptor antagonist (methoctramine) could block the suppression of HVSs induced by either systemic (IP) administration of an anticholinesterase drug [tetrahydroaminoacridine (THA)] or ICV infusion of oxotremorine in rats. Intrathalamic administration of oxotremorine at 3 and 15 μg in the NRT, and at 15 μg in the VPM suppressed HVSs. ICV oxotremorine at 30 and 100 μg and IP THA at 3 mg/kg decreased HVSs. ICV methoctramine at 100 μg increased HVSs and completely blocked the decrease in HVSs produced by oxotremorine 100 μg and THA 3 mg/kg. The results suggest that activation of muscarinic M2 acetylcholine receptors in thalamic nuclei (NRT and VPM) can suppress thalamocortical oscillations and that ICV or systemically administered drugs that activate either directly (oxotremorine and methoctramine) or indirectly (THA) the muscarinic M2 acetylcholine receptors may modulate neocortical HVSs via the thalamus.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(drugs that activate either directly or indirectly the muscarinic M2 acetylcholine receptors in the thalamic nuclei may modulate neocortical high-voltage spindles)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

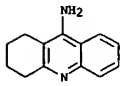
L11 ANSWER 20 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:805997 HCAPLUS
DOCUMENT NUMBER: 130:134115
TITLE: Tacrine and physostigmine block nicotinic receptors in Xenopus oocytes injected with Torpedo electroplaque membranes
AUTHOR(S): Canti, Carles; Bodas, Elena; Marsal, Jordi; Solsona, Carles
CORPORATE SOURCE: L'Hospitalet de Llobregat, Feixa Llarga s/n, Campus de Bellvitge. Pavello de Govern, Hospital de Bellvitge, Facultat de Medicina, Laboratori de Neurobiologia Cellular i Molecular, Departament de Biologia Cellular i Anatomia Patologica, Universitat de Barcelona, Barcelona, 08907, Spain
SOURCE: European Journal of Pharmacology (1998), 363(2/3), 197-202
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tacrine and physostigmine were tested for direct nicotinic actions on Xenopus oocytes microinjected with Torpedo electroplaque membranes. In this preparation, responses to acetylcholine arise 6-8 h after microinjection, due to the incorporation of nicotinic receptors into the plasma membrane by a process not involving protein synthesis. Currents elicited by acetylcholine (100-1000 μM) were recorded by two-electrode voltage clamping. Tacrine (1-1000 μM) and physostigmine (1-100 μM) exerted a potent, reversible block of the nicotinic receptors. The concentration-dependence curves fitted simple hyperbolas, suggesting a stoichiometry of 1:1 in the drug-channel interactions. Currents elicited by the highest acetylcholine concentration were inhibited by tacrine with maximal affinity, indicating an action at a site other than the ligand-binding domain. Inhibition was reduced at depolarizing potentials, which is consistent with a preferential interaction with the ligand-bound form of the receptor. Blockade by tacrine or physostigmine was accompanied by a concentration-dependent slowing of the desensitization, resembling the action of local anesthetics. These results could indicate a modulatory effect of these drugs on neurosecretion through nicotinic receptors.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tacrine and physostigmine block nicotinic receptors in Xenopus oocytes injected with Torpedo electroplaque membranes)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 20 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

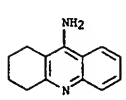
L11 ANSWER 21 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:706940 HCAPLUS
DOCUMENT NUMBER: 130:140589
TITLE: Pressor and bradycardic effects of tacrine and other acetylcholinesterase inhibitors in the rat
AUTHOR(S): Lazartigues, Eric; Freslon, Jean-Louis; Tellioglu, Tahir; Brefel-Courbon, Christine; Pelat, Michel; Tran, Marie-Antoinette; Montastruc, Jean-Louis; Rascol, Olivier
CORPORATE SOURCE: INSERM U317 et U455, Faculte de Medecine, Laboratoire de Pharmacologie Medicale et Clinique, Toulouse, 31073, Fr.
SOURCE: European Journal of Pharmacology (1998), 361(1), 61-71
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cardiovascular effects of three different acetylcholinesterase inhibitors: physostigmine, tacrine and rivastigmine injected by i.v. route were compared in freely moving Wistar rats. The three drugs significantly increased both systolic and diastolic blood pressure and decreased heart rate. Compared to physostigmine, a 20-fold higher dose of tacrine and a 40-fold higher dose of rivastigmine was necessary to induce a comparable pressor effect. Tacrine was chosen as a model to study the mechanisms underlying the cardiovascular effects of i.v. cholinesterase inhibitors. Atropine totally abolished while methylatropine did not affect tacrine pressor effects. Conversely, both drugs abolished tacrine-induced bradycardia. The α1-adrenoceptor antagonist prazosin or the vasopressin V1 receptor antagonist [β-mercapto-β,β-cyclopenta-methylenepropionyl1, O-Me-Tyr2, Arg8] vasopressin partially but significantly reduced tacrine pressor effect and mostly abolished it when administered concomitantly. The tacrine pressor response was inhibited in a dose-dependent manner by the i.c.v. administration of the non-selective muscarinic receptor antagonist atropine (ID50 = 1.45 μg), the muscarinic M1 receptor antagonist pirenzepine (ID50 = 4.33 μg), the muscarinic M2 receptor antagonist methoctramine (ID50 = 1.39 μg) and the muscarinic M3 receptor antagonist para-fluoro-hexahydro-sila-difenidol (ID50 = 31.19 μg). Central injection of such muscarinic receptor antagonists did not affect tacrine-induced bradycardia. Our results show that acetylcholinesterase inhibitors induce significant cardiovascular effects with a pressor response mediated mainly by the stimulation of central muscarinic M2 receptors inducing a secondary increase in sympathetic outflow and vasopressin release. Conversely, acetylcholinesterase inhibitor-induced bradycardia appears to be mediated by peripheral muscarinic mechanisms.

IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(mediation of tacrine and other acetylcholinesterase inhibitors pressor and bradycardic effects)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 21 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

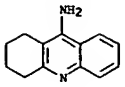
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 22 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:781529 HCAPLUS
DOCUMENT NUMBER: 130:261901
TITLE: Sensitivity to cholinergic drug treatments of aged rats with variable degrees of spatial memory impairment
AUTHOR(S): Stemmelin, Jeanne; Cassel, Jean-Christophe; Will, Bruno; Kelche, Christian
CORPORATE SOURCE: UMR 7521 ULP/CNRS, Laboratoire de Neurosciences Comportementales et Cognitives, Strasbourg, 67000, Fr.
SOURCE: Behavioural Brain Research (1999), 98(1), 53-66
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB As a first step, the present experiment aimed at characterizing learning and memory capabilities, as well as some motor and sensorimotor faculties, in aged (24-26.5 mo) Long-Evans female rats. As a second step, a psychopharmacol. approach was undertaken in order to examine the sensitivity of aged rats to muscarinic blockade and to cholinomimetic treatments. Young adult (3-5 mo) and aged rats were tested for beam-walking performance, locomotor activity in the home cage and an open field, and spatial learning/memory performance in a water maze and a radial maze. Spontaneous alternation rates were assessed in a T-maze. Statistical anal. discriminated between aged rats showing moderate impairment (AMI) and those showing severe impairment (ASI) in the water maze test. Beside their different degrees of impairment in the water maze, AMI and ASI rats were similarly (no significant difference) impaired in beam-walking capabilities, home cage activity and radial maze performance. In the spontaneous alternation task aged rats were not impaired and, in the open-field test, AMI rats were hypoactive, but not as much as ASI rats. Neither of the cognitive deficits was correlated with a locomotor or a sensorimotor variable, or with the body weight When tested in the radial maze, a low dose of scopolamine (0.1 mg/kg i.p.) produced memory impairments which were significant in AMI and ASI rats, but not in young rats. Combined injections of scopolamine and physostigmine (0.05 and 0.1 mg/kg) or tacrine (THA, 3 mg/kg) showed physostigmine (0.1 mg/kg) to compensate for the scopolamine-induced impairments only in AMI rats, whereas THA was efficient in both AMI and ASI rats. The results indicate: (i) that rats with different degrees of spatial memory impairment in the water maze are similarly hypersensitive to muscarinic blockade when tested in a radial maze test; and (ii) that under the influence of a dose of scopolamine which is subamnesic in young rats, aged rats respond to anticholinesterase treatments according to the level of performance achieved in the water maze: moderately impaired rats are sensitive to both physostigmine and THA, whereas more severely impaired rats are sensitive only to THA.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sensitivity to cholinergic drugs in aged rats with variable degrees of spatial memory impairment)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 22 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

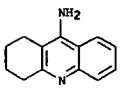


REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 23 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:663600 HCAPLUS
DOCUMENT NUMBER: 130:21887
TITLE: Conformational energy penalties of protein-bound ligands
AUTHOR(S): Bostrom, Jonas; Norrby, Per-Ola; Liljefors, Tommy
CORPORATE SOURCE: Department of Medicinal Chemistry, Royal Danish School of Pharmacy, Copenhagen, DK-2100, Den.
SOURCE: Journal of Computer-Aided Molecular Design (1998), 12(4), 383-396
CODEN: JCADEQ; ISSN: 0920-654X
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The conformational energies required for ligands to adopt their bioactive conformations were calculated for 33 ligand-protein complexes including 28 different ligands. In order to monitor the force field dependence of the results, two force fields, MM3* and AMBER*, were employed for the calcns. Conformational analyses were performed in vacuo and in aqueous solution by using the generalized Born/solvent accessible surface (GB/SA) solvation model. The protein-bound conformations were relaxed by using flat-bottomed Cartesian constraints. For about 70% of the ligand-protein complexes studied, the conformational energies of the bioactive conformations were calculated to be ≤3 kcal/mol. It is demonstrated that the aqueous conformational ensemble for the unbound ligand must be used as a reference state in this type of calcns. The calcns. for the ligand-protein complexes with conformational energy penalties of the ligand calculated to be larger than 3 kcal/mol suffer from uncertainties in the interpretation of the exptl. data or limitations of the computational methods. For example, in the case of long-chain flexible ligands (e.g. fatty acids), it is demonstrated that several conformations may be found which are very similar to the conformation determined by x-ray crystallog. and which display significantly lower conformational energy penalties for binding than obtained by using the exptl. conformation. For strongly polar mols., e.g. amino acids, the results indicate that further developments of the force fields and of the dielec. continuum solvation model are required for reliable calcns. on the conformational properties of this type of compds.

IT 321-64-2, Tacrine
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(conformational energy penalties of protein-bound ligands)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

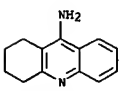


REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 24 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:660907 HCAPLUS
DOCUMENT NUMBER: 130:90332
TITLE: Effects of nicotine, pilocarpine, and tetrahydroaminoacridine on hippocampal theta waves in freely moving rabbits
AUTHOR(S): Yamamoto, Jyunji
CORPORATE SOURCE: Taiho Pharmaceutical, Pharmacological Research Laboratory, Kawauchi-Cho, Hiraishi, Ebisuno, Tokushima, 771-0194, Japan
SOURCE: European Journal of Pharmacology (1998), 359(2/3), 133-137
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

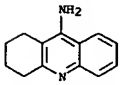
AB The effects of three cholinergic agents on hippocampal theta waves were investigated by analyzing electroencephalog. power spectra in freely moving rabbits. In the hippocampal spectra, nicotine (a nicotinic receptor agonist, 0.03 mg/kg) increased the theta wave frequency, but caused no change in its power. Pilocarpine (a muscarinic receptor agonist, 0.3 and 1.0 mg/kg) and tetrahydroaminoacridine (a cholinesterase inhibitor, 3.0 mg/kg) increased the power and deceased the frequency. These results suggest that the activating effect of nicotinic receptor agonists on the hippocampus may be different from that of muscarinic receptor agonists or cholinesterase inhibitors.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of nicotine, pilocarpine, and tetrahydroaminoacridine on hippocampal theta waves in freely moving rabbits)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



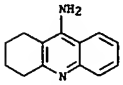
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 25 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:648141 HCAPLUS
DOCUMENT NUMBER: 130:60444
TITLE: New cholinergic therapies: treatment tools for the psychiatrist
AUTHOR(S): Tune, Larry E.; Sunderland, Trey
CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences; Wesley Woods Center on Aging at Emory University, Emory University School of Medicine, Atlanta, GA, 30329, USA
SOURCE: Journal of Clinical Psychiatry (1998), 59(Suppl. 13), 31-35
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 21 refs., describing the current status of therapy with acetylcholine-enhancing compds. in the management of patients with Alzheimer's disease. The focus is on pivotal articles investigating the role of cholinergic augmentation strategies, including precursor loading and acetylcholinesterase (AChE) inhibitors, in the management of cognitive and noncognitive symptoms of Alzheimer's disease. Precursor loading strategies have been for the most part unimpressive. By contrast, studies with AChE inhibitors--tacrine and donepezil--have been promising. For patients in whom hepatotoxicity and gastrointestinal side effects were not problematic, tacrine improves cognitive performance and selected secondary psychiatric symptoms and delays nursing home placement. Donepezil, recently approved for use in mild to moderate Alzheimer's disease, appears to be less toxic and better tolerated than tacrine. It improves performance on cognitive testing and, in one preliminary investigation, demonstrated a sustained effect over several years. Therapy with AChE inhibitors provides modest significant symptomatic improvement in patients with mild to moderate Alzheimer's disease.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Alzheimer's disease of humans treatment by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



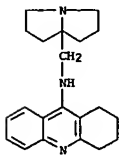
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 26 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:616564 HCAPLUS
DOCUMENT NUMBER: 130:10276
TITLE: Caffeine based measures of CYP 1A2 activity correlate with oral clearance of tacrine in patients with Alzheimer's disease
AUTHOR(S): Fontana, Robert J.; deVries, Tina M.; Woolf, Thomas F.; Knapp, Margaret J.; Brown, As; Kaminsky, Laurence S.; Tang, Bing-Kuo; Foster, Norman L.; Brown, Richard R.; Watkins, Paul B.
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor, MI, 48109, USA
SOURCE: British Journal of Clinical Pharmacology (1998), 46(3), 221-228
CODEN: BCPHEM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study tested the potential utility of caffeine based probes of CYP1A2 enzyme activity in predicting the pharmacokinetics of tacrine in patients with Alzheimer's disease. The pharmacokinetics of a single 40 mg oral dose of tacrine were measured in 19 patients with Alzheimer's disease. Each patient also received 2 mg kg-1 [13C-3-methyl] caffeine orally and had breath and urine samples collected. Tacrine oral clearance (CL F-1 kg-1), which varied 15-fold among the patients, correlated significantly with the 2 h total production of 13CO2 in breath (r=0.56, P=0.01), and with each of two commonly used urinary caffeine metabolite ratios: the "paraxanthine/caffeine ratio" (1,7X + 1, 7U/1,3,7X) (r=0.76, P=0.0002) and the "caffeine metabolic ratio" (AFMU + 1X + 1U/1, 7U)(r=0.76, P=0.0001). These observations support a central role for CYP1A2 in the in vivo disposition of tacrine and the potential for drug interactions when tacrine treated patients receive known inducers or inhibitors of this enzyme. The magnitude of the correlations we observed, however, are probably
not sufficient to be clin. useful in individualizing tacrine therapy.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(caffeine based measures of CYP1A2 activity correlate with oral tacrine clearance in humans with Alzheimer's disease)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:558082 HCAPLUS
DOCUMENT NUMBER: 129:260300
TITLE: Synthesis and muscarinic activity of a series of quinolines and naphthalenes with a 1-azabicyclo[3.3.0]octane moiety
AUTHOR(S): Suzuki, Tomoo; Usui, Toshinao; Oka, Mitsuru; Suzuki, Tsunemasa; Kataoka, Tadashi
CORPORATE SOURCE: Drug Discovery Research Laboratory, Sanwa Kagaku Kenkyusho Co., Ltd., Mie, 511-0406, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1998), 46(8), 1265-1273
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to discover a medicine effective against Alzheimer's disease, a series of quinoline derivs. having a characteristic 1-azabicyclo[3.3.0]octane amine ring, were synthesized and their pharmacol. evaluated. Acetylcholine esterase inhibitory activities of these derivs. were unexpectedly weak. Tests for central nervous muscarinic cholinergic receptor binding affinity indicated that these compds. had higher affinities to muscarinic M1 receptors than to M2 receptors. A series of naphthalene derivs. substituted with the 1-azabicyclo[3.3.0]octane ring were also synthesized and muscarinic M1 and M2 receptor binding affinity determined These compds. had much higher affinity for M1 receptors than the quinoline derivs., and 1-[N-(1-azabicyclo[3.3.0]octan-5-yl)methyl-N-methylamino]-4-nitronaphthalene showed the highest affinity and selectivity. The ability of this compound to improve cognitive function was assessed using the passive avoidance test in scopolamine-induced mice.
IT 213383-42-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and muscarinic activity of azabicyclooctylalkylquinolines and -naphthalenes)
RN 213383-42-7 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-N-[(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



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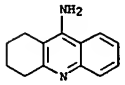
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 27 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 28 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:557356 HCAPLUS
DOCUMENT NUMBER: 129:270523
TITLE: Sabcomeline (SB-202026), a functionally selective M1 receptor partial agonist, reverses delay-induced deficits in the T-maze
AUTHOR(S): Hatcher, J. P.; Loudon, J. M.; Hagan, J. J.; Clark, M. S. G.
CORPORATE SOURCE: Neurosciences Research, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Essex, CM19 5AW, UK
SOURCE: Psychopharmacology (Berlin) (1998), 138(3/4), 275-282
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sabcomeline, (SB-202026 [R-(Z)-α-(methoxyimino)-1-azabicyclo [2.2.2]octane-3-acetonitrile]), a functionally selective muscarinic M1 receptor partial agonist, was tested in rats trained to perform a delayed, reinforced alternation task in a T maze, a test of short-term spatial memory. For comparison the cholinesterase inhibitor tacrine (THA-9-amino-1,2,3,4-tetrahydroaminoacridine) and the non-selective muscarinic receptor agonist RS86 (2-ethyl-8-methyl-2,8 diazospiro [4.5]-decane-1,3-dione hydrobromide) were also tested and all three compds. were also compared using a conditioned taste aversion (CTA) task. Sabcomeline (0.001-1.0 mg/kg IP) significantly reversed the T-maze choice accuracy deficit induced by a 20-s delay at 0.03 and 0.1 mg/kg. RS86 (0.1-3.0 mg/kg IP) reversed the deficit at 1.0 mg/kg and THA (0.1-3.0 mg/kg IP) had no effect at any dose. All three compds. induced conditioned taste aversion with min. EDs (MED) of 0.3, 1.0 and 3.0 mg/kg, resp. The results show that sabcomeline reverses delay induced deficits in T-maze choice accuracy in a rewarded alternation task at doses approx. 10 times lower than those required to induce conditioned taste aversion. RS86 was equipotent in both tests. These data support the findings of clin. studies which have shown that SB-202026 provides significant symptomatic improvement in patients with probable Alzheimer's disease at doses which do not induce cholinergic side effects.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M1 receptor partial agonist sabcomeline reverses delay-induced deficits in the T-maze and possible therapeutic application for Alzheimer's disease)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

L11 ANSWER 28 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

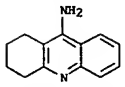
L11 ANSWER 29 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:490540 HCAPLUS
DOCUMENT NUMBER: 129:131258
TITLE: Acetylcholinesterase inhibitors in combination with muscarinic agonists for the treatment of Alzheimer's disease or other disorders involving cholinergic hypofunction
INVENTOR(S): Schwarz, Roy Douville; Callahan, Michael James
PATENT ASSIGNEE(S): Warner-Lambert Co., USA; Schwarz, Roy Douville; Callahan, Michael James
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830243	A1	19980716	WO 1997-US23792	19971229
W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857168	A1	19980803	AU 1998-57168	19971229
ZA 9800118	A	19980708	ZA 1998-118	19980107
PRIORITY APPLN. INFO.:			US 1997-34059P P	19970108
			US 1997-65886P P	19971117
			WO 1997-US23792 W	19971229

AB New compns. of matter and a method for treating bodily disorders involving cholinergic hypofunction, e.g. Alzheimer's disease, in a mammal are disclosed. The compns. comprise a combination of an acetylcholinesterase inhibitor and a muscarinic agonist. The method comprises administration of the combination to a mammal. The invention demonstrates that the combination of an acetylcholinesterase inhibitor and a muscarinic agonist can be safely administered, that doses of each agent which by themselves showed no activity yielded pos. responses and minimal side effects in combination, and that the active dose range for both agents could be widened when used in combination. These results imply that the combined treatment may eliminate the need to individually titrate doses and also increase the separation between efficacy and adverse events.

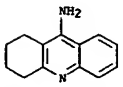
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholinesterase inhibitor-muscarinic agonist combination for treatment of Alzheimer's disease or other disorder involving cholinergic hypofunction)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 29 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



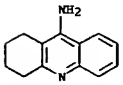
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 30 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:409601 HCAPLUS
DOCUMENT NUMBER: 129:170379
TITLE: Tetrahydroaminoacridine, a cholinesterase inhibitor, and D-cycloserine, a partial NMDA receptor-associated glycine site agonist, enhances acquisition of spatial navigation
AUTHOR(S): Riekkinen, Paavo, Jr.; Ikonen, Sami; Riekkinen, Minna
CORPORATE SOURCE: Department of Neurology, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: NeuroReport (1998), 9(7), 1633-1637
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study examines the efficacy of single and combined treatments with an anticholinesterase, tetrahydroaminoacridine (THA, i.p.), and a glycine-B site partial agonist, D-cycloserine (DCS, i.p.) to alleviate water maze (WM) spatial navigation defect induced by medial septal (MS) lesion. THA 3 and DCS at 3 or 10 mg/kg improved acquisition of the WM test, but only DCS improved spatial bias. These drugs had no effect on consolidation. A combination of THA 3 and DCS 10 mg/kg enhanced WM acquisition more effectively than either of the treatments on their own. This suggests that combined modulation of acetylcholine and NMDA mechanisms may have greater therapeutic effect to stimulate cognitive dysfunctions.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tetrahydroaminoacridine and D-cycloserine enhance acquisition of spatial navigation in rats)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

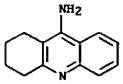
L11 ANSWER 31 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:384767 HCAPLUS
DOCUMENT NUMBER: 129:156804
TITLE: Effects of AF102B and tacrine on delayed match-to-sample in monkeys
AUTHOR(S): O'neill, Joseph; Fitten, L. Jaime; Siembieda, Douglas; Halgren, Eric; Kim, Ellen; Fisher, Abraham; Perryman, Kent
CORPORATE SOURCE: Department of Veterans Affairs Wadsworth Medical Center, Los Angeles, CA, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1998), 22(4), 665-678
CODEN: PNPPD7; ISSN: 0278-5846
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1. Object working memory, a function which declines in aging and dementia, was tested in young and aged pretrained monkeys using a delayed match-to-sample task. 2. During drug treatment, monkeys were given the m 1 muscarinic agonist AF102B (0.1-2.1 mg/kg i.m.), the cholinesterase inhibitor tacrine (0.5-2.0 mg/kg p.o.), or vehicle controls in a repeated measures design to assess putative cognitive enhancement. 3. Both agents improved task performance in both young and aged monkeys, AF102B yielding equivalent or greater, and less variable, improvement than tacrine. 4. AF102B may represent a low-toxicity alternative to tacrine for the treatment of age-related memory disorders.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of AF102B and tacrine on memory enhancement in aging monkeys)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 32 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:362251 HCAPLUS
DOCUMENT NUMBER: 129:117689
TITLE: Xanomeline compared to other muscarinic agents on stimulation of phosphoinositide hydrolysis in vivo and other cholinomimetic effects
AUTHOR(S): Bymaster, Frank P.; Carter, Petra A.; Peters, Steven C.; Zhang, Wei; Ward, John S.; Mitch, Charles H.; Calligaro, David O.; Whitesitt, Celia A.; DeLapp, Neil; Shannon, Harlan E.; Rimvall, Karin; Jeppesen, Lone; Sheardown, Malcolm J.; Fink-Jensen, Anders; Sauerberg, Per
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Neuroscience Research, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Brain Research (1998), 795(1,2), 179-190
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activation of muscarinic m1 receptors which are coupled to the phosphoinositide (PI) second messenger transduction system is the initial objective of cholinergic replacement therapy in Alzheimer's disease. Thus, we evaluated the ability of the selective muscarinic receptor agonist (SMRA) xanomeline to stimulate in vivo phosphoinositide (PI) hydrolysis and compared it to a number of direct acting muscarinic agonists, two cholinesterase inhibitors and a putative m1 agonist/muscarinic m2 antagonist. Using a radiometric technique, it was determined that administration of xanomeline robustly stimulated in vivo PI hydrolysis and the effect was blocked by muscarinic antagonists, demonstrating mediation by muscarinic receptors. The non-selective muscarinic agonists pilocarpine, oxotremorine, RS-86, S-aceclidine, but not the less active isomer R-aceclidine, also effectively stimulated PI hydrolysis in mice. Amongst the putative m1 agonists, thiopilocarpine, hexylthio-TZTP as well as xanomeline effectively stimulated PI hydrolysis, but milameline, WAL 2014, SKB 202026 and PD 142505 did not significantly alter PI hydrolysis. Furthermore, WAL 2014 and SKB 202026 inhibited agonist-induced PI stimulation, suggesting that they act as antagonists at PI-coupled receptors in vivo. The cholinesterase inhibitors, tacrine and physostigmine, and the mixed muscarinic m1 agonist/m2 antagonist LU25-109 did not activate in vivo PI hydrolysis. Xanomeline, hexylthio-TZTP and thiopilocarpine were relatively free of cholinergic side effects, whereas milameline, WAL 2014 and SKB 202026 produced non-selective effects. Therefore, these data demonstrate that xanomeline selectively activates in vivo PI hydrolysis, consistent with activation of biochem. processes involved in memory and cognition and xanomeline's beneficial clin. effects on cognition in Alzheimers patients.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(xanomeline compared to other muscarinic agents on stimulation of phosphoinositide hydrolysis in vivo and other cholinomimetic effects)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

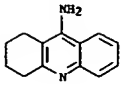
L11 ANSWER 32 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

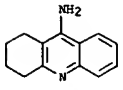
L11 ANSWER 33 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:306008 HCAPLUS
DOCUMENT NUMBER: 129:76367
TITLE: Central cardiovascular effects of tacrine in the conscious dog: a role for catecholamines and vasopressin release
AUTHOR(S): Allal, Cuider; Lazartigues, Eric; Tran, Marie-Antoinette; Brefel-Courbon, Christine; Gharib, Claude; Montastruc, Jean-Louis; Rascol, Olivier
CORPORATE SOURCE: INSERM U455 et U317, Laboratoire de Pharmacologie Medicale et Clinique, Faculte de Medecine, Toulouse, 31073, Fr.
SOURCE: European Journal of Pharmacology (1998), 348(2/3), 191-198
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Centrally acting cholinergic agents are currently reported to increase blood pressure in various species through the stimulation of muscarinic cholinoceptors. Moreover, several cardiovascular adverse effects have been reported from clin. studies. The aim of this study was to investigate the effects of tacrine, an acetylcholinesterase inhibitor which has been reported to have therapeutic potential in Alzheimer's disease, on blood pressure and two vasopressor systems (sympathetic and vasopressinergic) in Beagle dogs. I.v. (i.v.) tacrine (2 mg kg-1) induced, in conscious and anesthetized dogs, an increase in systolic and diastolic blood pressure, accompanied by bradycardia. This increase was dose-dependent with a peak effect at 1.5 min following administration. Tacrine also induced an increase in noradrenaline, adrenaline and vasopressin plasma levels. Pretreatment with the muscarinic receptor antagonist, atropine (2 mg kg-1, i.v.), abolished the pressor response to i.v. injection of tacrine while pretreatment with the peripheral muscarinic receptor antagonist, methylscopolamine (0.2 mg kg-1, i.v.), did not alter the increase in blood pressure. Similarly, noradrenaline and adrenaline changes in plasma levels were not modified by methylscopolamine but were abolished by atropine pretreatment. A similar tendency although not significant was observed for vasopressin plasma levels. The present results demonstrate that in dogs, tacrine (2 mg kg-1, i.v.) stimulates central muscarinic cholinoceptors to increase blood pressure through activation of the two components of the sympathetic nervous system (i.e., neuronuronal noradrenergic and the neurohormonal adrenergic pathways) as well as through increasing noradrenaline, adrenaline and vasopressin plasma levels.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(role for catecholamines and vasopressin release in central cardiovascular effects of tacrine in the conscious dog)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 33 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



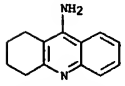
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 34 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:206156 HCAPLUS
DOCUMENT NUMBER: 129:478
TITLE: Cardiovascular effects of centrally injected tetrahydroaminoacridine in conscious normotensive rats
AUTHOR(S): Savci, Vahide; Gurun, M. Sibel; Cavun, Sinan; Ulus, Ismail H.
CORPORATE SOURCE: Medical Faculty, Department of Pharmacology, Uludag University, Bursa, TR-16059, Turk.
SOURCE: European Journal of Pharmacology (1998), 346(1), 35-41
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In freely moving rats, intracerebroventricularly (i.c.v.) injected tetrahydroaminoacridine (10, 25, 50 μg) increased blood pressure and decreased heart rate in a dose- and time-dependent manner. I.v. (i.v.) tetrahydroaminoacridine (1 and 3 mg/kg) also increased blood pressure. Atropine sulfate (10 μg; i.c.v.) pretreatment greatly attenuated the blood pressure response to i.c.v. tetrahydroaminoacridine while mecamylamine (50 μg; i.c.v.) failed to change the pressor effect. Neither atropine sulfate nor mecamylamine pretreatment affected the bradycardia induced by tetrahydroaminoacridine. However, the bradycardic response was completely blocked by atropine methylnitrate (2 mg/kg; i.p.) pretreatment. The pressor response to i.c.v. tetrahydroaminoacridine was associated with a several-fold increase in plasma levels of vasopressin, adrenaline and noradrenaline, but not of plasma renin. Pretreatment with prazosin (0.5 mg/kg; i.v.) attenuated the pressor effect without changing the bradycardia. Vasopressin V1 receptor antagonist [β-mercapto-β,β-cyclopentamethylenepropionyl1,O-Me-Tyr2-Arg8]vasopressin (10 μg/ kg; i.v.) pretreatment also partially inhibited the pressor response to i.c.v. tetrahydroaminoacridine and abolished the bradycardia. Tetrahydroaminoacridine's cardiovascular effects were completely blocked when rats were pretreated with prazosin plus vasopressin antagonist. The data show that tetrahydroaminoacridine increases blood pressure in normotensive freely moving rats by activating central muscarinic cholinergic transmission. Increases in plasma catecholamines and vasopressin are both involved in this response. The tetrahydroaminoacridine-induced reduction in heart rate appears to be due to the increase in vagal tone and plasma vasopressin.
IT 321-64-2
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cardiovascular effects of centrally injected tetrahydroaminoacridine in conscious normotensive rats mediated by muscarinic neurotransmission in relation to hormone response)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 35 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:169303 HCAPLUS
DOCUMENT NUMBER: 128:278876
TITLE: Effects of NIK-247 and tacrine on muscarinic receptor subtypes in rats
AUTHOR(S): Kojima, Jun; Onodera, Kenji
CORPORATE SOURCE: Omiya Research Laboratory, Nikken Chemicals Co., Ltd., Saitama, 330, Japan
SOURCE: General Pharmacology (1998), 30(4), 537-541
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to compare the effect of NIK-247 on muscarinic receptor subtypes with that of tacrine (THA) in rats. NIK-247 and tacrine dose dependently inhibited the binding of [3H]pirenzepine (M1), [3H]AF-DX 384 (M2), and [3H]4-DAMP (M3). The IC50 values for NIK-247 were 4.4+10-6 M, 1.1+10-5 M, and 1.5+10-5 M, resp., whereas those for tacrine were 5.8+10-7 M, 2.0+10-6 M, and 5.8+10-6 M, resp. Gpp[NH]p, a GTP analog, slightly shifted the curve of displacement of [3H]AF-DX 384 binding for NIK-247 to the right. However, Gpp[NH]p did not shift the curve of displacement of [3H]pirenzepine and [3H]4-DAMP binding to the right. NIK-247 moderately decreased the rate of beating in right atrial prepns., but did not decrease it below 50% of control level. These findings indicate that NIK-247 is an M1 antagonist, M2 partial agonist, and M3 antagonist.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of effects of NIK-247 vs. tacrine on muscarinic receptor subtypes in rats)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

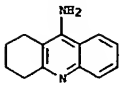
L11 ANSWER 36 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:164220 HCAPLUS
DOCUMENT NUMBER: 128:238908
TITLE: Comparative biomembrane permeation of tacrine using Yucatan minipigs and domestic pigs as the animal model
AUTHOR(S): Gore, Anuradha V.; Liang, Alfred C.; Chien, Yie W.
CORPORATE SOURCE: Controlled Drug-Delivery Research Center, Rutgers College of Pharmacy, Piscataway, NJ, 08854., USA
SOURCE: Journal of Pharmaceutical Sciences (1998), 87(4), 441-447
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tacrine (THA), a centrally acting **acetylcholine**-esterase inhibitor, is presently administered orally for the treatment of Alzheimer's disease (AD). However, its low bioavailability (i.e., 17%) and short half-life (2-4 h) demand the search for alternative routes of administration. The primary objective of this study was to assess the potential of absorptive mucosae and skin as routes for improving the systemic delivery of THA. The Yucatan minipig, which has been used increasingly in biomedical research as a useful model for humans, and the domestic pig, which is available at low cost, were evaluated for their suitability as animal model. Permeation kinetics of THA across various absorptive mucosae (nasal, buccal, sublingual, and rectal) of both species of swine were studied in the hydrodynamically well-calibrated Valia-Chien permeation cells. For comparison, permeation through various intestinal segments (duodenum, jejunum, and ileum) was also measured. Results indicated that both species display similar permeation characteristics. However, the data obtained for the domestic pigs shows lower intra- and interanimal variabilities than that of the Yucatan minipigs. The nasal mucosa was found to have the highest permeability, while the buccal mucosa had the lowest among the absorptive mucosae. The intrinsic permeabilities and diffusivity of THA across the four absorptive mucosae were not significantly different between species but lower than that for the intestinal segments for both species. Using dorsal skin as the model, the skin permeation of THA was also investigated and the results indicated that the domestic swine has a significantly higher skin permeability than the Yucatan minipig, with more than a 2-fold difference in intrinsic permeabilities. The intrinsic permeability, partition coefficient, and diffusivity for domestic pig skin are very similar to that for human cadaver skin. Considering the potential of bypassing the hepatic "first-pass" elimination, the absorptive mucosae may be useful routes for systemic delivery of THA to achieve improved bioavailability. With addnl. advantages of lower variability, ease of membrane excision, good accessibility, and lower cost, it is concluded that the domestic swine is a better animal model than the Yucatan minipig for preclin. studies on the systemic delivery of tacrine.

IT **321-64-2**, Tacrine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(comparative biomembrane permeation of tacrine using Yucatan minipigs and domestic pigs as the animal model)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 36 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



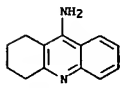
L11 ANSWER 37 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:101603 HCAPLUS
DOCUMENT NUMBER: 128:213287
TITLE: Tacrine administration enhances extracellular **acetylcholine** in vivo and restores the cognitive impairment in aged rats
AUTHOR(S): Scali, Carla; Giovannini, Maria Grazia; Prosperi, Costanza; Bartolini, Luciano; Pepeu, Giancarlo
CORPORATE SOURCE: Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, 50134, Italy
SOURCE: Pharmacological Research (1997), 36(6), 463-469
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of oral tacrine administration on cortical and hippocampal extracellular **acetylcholine** (ACh) levels was investigated by a microdialysis technique, coupled to a HPLC method, in 6- and 22-24-mo-old rats. To assess whether the increase in extracellular ACh levels was associated with an improvement in the age-related cognitive impairment, the object recognition and step-trough passive avoidance tests were carried out in the treated rats. The extracellular ACh levels measured in the cortex and hippocampus of aged rats without cholinesterase inhibitor in the perfusion Ringer solution were 39 and 54% lower, resp., than in the young rats. At the dose of 3 mg kg-1, tacrine brought about a three- to four-fold increase in extracellular ACh levels, both in young and aged rats, which peaked 60-80 min after administration and disappeared within the next 60 min. At the same dose, tacrine caused a twofold increase in extracellular ACh levels in the hippocampus of young rats and a sixfold increase in aged rats. The absolute ACh levels at the peak in aged rats were not significantly different from those of young rats. In the object recognition test, aging rats were unable to discriminate between the familiar and novel object. Discrimination was restored by the administration of tacrine at the dose of 1 and 3 mg kg-1, but not 0.3 mg kg-1 given 30 min before the first trial. Tacrine (3 mg kg-1 p.o.) administered to aging rats before the training trial significantly improved the acquisition of the passive avoidance conditioned response. The findings demonstrate that tacrine increased both cortical and hippocampal extracellular ACh levels and improved behavioral functions in aged rats.

IT **321-64-2**, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tacrine enhances central extracellular **acetylcholine** and restores cognitive impairment in aging)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 37 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

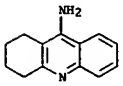


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 38 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:67838 HCAPLUS
DOCUMENT NUMBER: 128:201248
TITLE: Kinetics of muscarinic reduction of IsAHP in hippocampal neurons: effects of acetylcholinesterase inhibitors
AUTHOR(S): Zhang, Y.; Carlen, P. L.; Zhang, L.
CORPORATE SOURCE: Playfair Neuroscience Unit, Department of Medicine (Neurology), Toronto Hospital Research Institute, Bloorview Epilepsy Program, University of Toronto, Toronto, ON, M5T 2S8, Can.
SOURCE: Journal of Neurophysiology (1997), 78(6), 2999-3007
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present expts. were designed to elucidate the time frame in which an evoked cholinergic impulse increases the Ca2+-dependent K+ current (IsAHP) in hippocampal CA1 neurons, and to determine to what extent acetylcholinesterase (AChE) inhibitors enhance the efficacy of the cholinergic impulse. Whole cell voltage-clamp recordings were performed on hippocampal CA1 neurons of rat brain slices and IsAHPs were evoked by constant depolarizing pulses. Cholinergic afferent fibers in stratum oriens were stimulated elec. and the time interval between the afferent stimulus and the depolarizing pulse was varied from 1 to 30 s. In slices perfused with the standard external medium, the afferent stimulus caused a profound decrease in the following IsAHP only when the stimulus preceded the depolarizing pulse by 1-2 s. The stimulus was without effects on the IsAHP when applied ≥5s before the depolarizing pulse. The effects of the afferent stimulus were greatly enhanced in CA1 neurons exposed to the catalytic AChE inhibitors neostigmine, physostigmine, or 9-amino-1,2,3,4-tetrahydro-acridine. A substantial decrease in the IsAHP was observed even when the stimulus preceded the depolarizing pulse by ≥30 s. However applications of peripheral site AChE inhibitors decamethonium and propidium caused only minor or no enhancement of the IsAHP reduction after the afferent stimulus. We suggest in physiol. conditions that muscarinic modulation of ionic conductances of CNS neurons has a limited time course after a cholinergic impulse and that the modulation is greatly enhanced and prolonged when catalytic activities of AChEs are suppressed pharmacol.

IT 321-64-2, 9-Amino-1,2,3,4-tetrahydro-acridine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kinetics of muscarinic reduction of Ca2+-dependent K+ current in hippocampal neurons and effects of acetylcholinesterase inhibitors)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

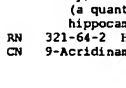


L11 ANSWER 38 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 39 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:787391 HCAPLUS
DOCUMENT NUMBER: 128:110753
TITLE: A quantitative pharmacological study of the cholinergic depolarization of hippocampal pyramidal cells in rat brain slices
AUTHOR(S): Scuvee-Moreau, J.; Seutin, V.; Dresse, A.
CORPORATE SOURCE: Laboratory of Phamacology, Institute of Pathology, University of Liege, Sart-Tilman, Belg.
SOURCE: Archives of Physiology and Biochemistry (1997), 105(4), 365-372
CODEN: APBIF5; ISSN: 1381-3455
PUBLISHER: Swets & Zeitlinger B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intracellular recordings were performed in rat brain slices and the pharmacol. of the depolarizing effect of cholinomimetic drugs on hippocampus CA1 pyramidal cells was quant. investigated. Acetylcholine (ACh) and muscarine induced a concentration-dependent depolarization of these cells. The EC50 values were resp. 159±54 μM and 0.7±0.15 μM. Physostigmine (1 μM) or tacrine (1 μM) induced a marked shift in the concentration-response curve for ACh. Both drugs were equipotent in this respect. The EC50 values for ACh became, resp., 2,4±1.5 μM and 3±0.9 μM. The depolarizing effect of ACh was completely blocked by atropine, confirming the involvement of a receptor of the muscarinic type. In order to determine the subtype of muscarinic receptor involved, the EC50 values of muscarine were determined in the presence of atropine (100 nM), pirenzepine (1 μM) or AFDX116 (10 μM). The deduced pKB for the antagonists were, resp., 8.9, 7.4 and 6.5. Comparison with binding data suggests that M1 receptors play a prominent role in the depolarizing effect of cholinomimetic drugs on CA1 pyramidal cells.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(a quant. pharmacol. study of the cholinergic depolarization of hippocampal pyramidal cells in rat brain slices)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

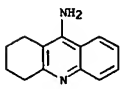


REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 40 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:731232 HCAPLUS
DOCUMENT NUMBER: 128:20119
TITLE: Imaging of nicotinic and muscarinic receptors in Alzheimer's disease: effect of tacrine treatment
AUTHOR(S): Nordberg, Agneta; Lundqvist, Hans; Hartvig, Per; Andersson, Jesper; Johansson, Monika; Hellstrom-Lindahl, Ewa; Langstrom, Bengt
CORPORATE SOURCE: Dep. Clinical Neuroscience Family Medicine, Division of Nicotine Research, Karolinska institutet, Huddinge Univ. Hospital, Huddinge, S-141 86, Swed.
SOURCE: Dementia and Geriatric Cognitive Disorders (1997), 8(2), 78-84
CODEN: DGCDFX; ISSN: 1420-8008
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Functional imaging techniques offer new possibilities for further understanding of changes in functional correlates of structural and biol. changes in dementia disorders like Alzheimer's disease (AD). Regional disturbances in glucose metabolism and cerebral blood flow are known to occur in AD brains and probably roughly correlate to changes in neurotransmitter activities. A proper estimate would be to visualize the neuroreceptors themselves. In this study the cholinergic nicotinic and muscarinic receptors were studied in brain by positron emission tomog. (PET). The rate constant k2' (s)(-)11C-nicotine was significantly higher (+43%) in temporal cortex of AD patients compared to controls (P<0.017) indicating a lower binding of 11C-nicotine in AD brains compared to controls. Treatment with the cholinesterase inhibitor tacrine (80 mg daily) during 3 mo to AD patients resulted in a mean plasma concentration of 7.7 ± 0.8 ng/mL and a corresponding inhibition of the cholinesterase activity in plasma by 34 ± 5%. A significantly lower k2' (increased binding) for 11C-nicotine binding (-15%; p , 0.006) was obtained in the temporal cortex after 3 mo of treatment compared to prior treatment. The muscarinic antagonist 11C-benztropine was used to visualize muscarinic receptors and the binding capacity of 11C-benztropine (KR) was found to be decreased in the temporal cortex after 3 mo of tacrine treatment.

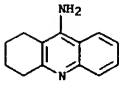
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(imaging of nicotinic and muscarinic receptors in Alzheimer's disease: effect of tacrine treatment)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 40 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 41 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:708159 HCAPLUS
DOCUMENT NUMBER: 128:10240
TITLE: Repeated administration of tacrine to normal rats: effects on cholinergic, glutamatergic, and GABAergic receptor subtypes in rat brain using receptor autoradiography
AUTHOR(S): Sihver, Wiebke; Gunther, Peter; Schliebs, Reinhard; Bigl, Volker
CORPORATE SOURCE: Paul Flechsig Institute for Brain Research, Department of Neurochemistry, University of Leipzig, Leipzig, D-04109, Germany
SOURCE: Neurochemistry International (1997), 31(5), 693-703
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine, a potent acetylcholinesterae inhibitor, has been reported to improve cognitive function in patients with Alzheimer's disease. The present investigation was conducted to elucidate in vivo any interaction between tacrine-induced cortical cholinergic hyperactivity and glutamatergic and GABAergic neurotransmission, which might influence the therapeutic potential of tacrine. Seven days after a daily dosage of 10mg/kg tacrine i.p. quant. receptor autoradiog. was performed in coronal sections throughout the brain. Repeated administration of tacrine resulted in decreased binding to high-affinity choline uptake, nicotinic and M2-muscarinic acetylcholine receptor sites in a number of cortical regions, while redns. in M1-muscarinic receptor binding were restricted to the cingulate and entorhinal cortex as well as caudate-putamen. Moreover, tacrine injections decreased cortical AMPA receptor binding throughout the brain, while NMDA, kainate, and GABAA receptor binding remained unchanged. Tacrine administration alters cortical AMPA receptor binding in the opposite direction to that observed in patients with Alzheimer's disease, suggesting that tacrine may exert a reversal in up/down-regulation of cortical glutamate receptor subtypes in Alzheimer patients. However, the drug-induced redns. in cortical high-affinity choline uptake sites as well as in nicotinic and in muscarinic acetylcholine receptor binding might partially counteract the cognition-enhancing effects of tacrine produced by acetylcholinesterase inhibition.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tacrine effects on cholinergic, glutamatergic, and GABAergic receptor subtypes in brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

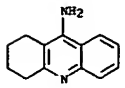


L11 ANSWER 41 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 42 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:645693 HCAPLUS
DOCUMENT NUMBER: 127:257399
TITLE: Development and characterization of a new model of tacrine-induced hepatotoxicity: role of the sympathetic nervous system and hypoxia-reoxygenation
AUTHOR(S): Stachlewitz, Robert F.; Arteel, Gavin E.; Raleigh, James A.; Connor, Henry D.; Mason, Ronald P.; Thurman, Ronald G.
CORPORATE SOURCE: Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 282(3), 1591-1599
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine is an acetylcholinesterase inhibitor approved for the treatment of Alzheimer's disease. Unfortunately, reversible hepatotoxicity in .apprx.30% of patients at therapeutic doses limits clin. use. The purpose of this study was to develop and characterize a model of tacrine hepatotoxicity to begin to understand the mechanisms of injury. Rats were given tacrine (10-50 mg/kg, intragastrically) and killed 24 h later. An increase in serum aspartate aminotransferase was observed up to 35 mg/kg and histol. revealed pericentral necrosis and fatty changes. Aspartate aminotransferase was increased from 12 to 24 h and returned to control values by 32 h. Livers were perfused in a nonrecirculating system to measure oxygen uptake and trypan blue was infused at the end of each experiment to evaluate tissue perfusion. Time for trypan blue to distribute evenly throughout the liver 3 h after tacrine treatment was significantly increased (6.9 ± 1.3 min) compared to controls (1.0 ± 0.3 min) reflecting decreased tissue perfusion. Tacrine also significantly increased the binding of a hypoxia marker, pimonidazole, in pericentral regions almost 3-fold, and increased portal pressure in vivo significantly. It is hypothesized that tacrine, by inhibiting acetylcholine breakdown in the celiac ganglion, increases sympathetic activity in the liver leading to vascular constriction, hypoxia, and liver injury. To test this hypothesis, the hepatic nerve was severed and animals were allowed to recover before tacrine treatment. This procedure significantly reduced serum aspartate aminotransferase, time of dye distribution, pimonidazole binding, and portal pressure. Furthermore, a free radical adduct was detected with spin trapping and ESR spectroscopy 8 h after tacrine treatment, providing evidence for reoxygenation. When catechin (100 mg/kg, i.p.), a free radical scavenger, was given before tacrine, injury was decreased by .apprx.45%. Furthermore, feeding 5% arginine in the diet significantly reduced portal pressure and time of dye distribution. These data are consistent with the hypothesis that tacrine hepatotoxicity is a hypoxia-reoxygenation injury mediated through the sympathetic nervous system.
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(development and characterization of new model of tacrine-induced hepatotoxicity in relation to sympathetic nervous system and hypoxia-reoxygenation)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

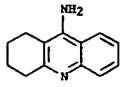
L11 ANSWER 42 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

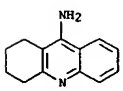
L11 ANSWER 43 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:586561 HCAPLUS
DOCUMENT NUMBER: 127:272635
TITLE: Effect of tacrine on intracellular calcium in cholinergic SN56 neuronal cells
AUTHOR(S): Dolezal, Vladimir; Lisa, Vera; Tucek, Stanislav
CORPORATE SOURCE: Institute of Physiology, Academy of Sciences of the Czech Republic, Videnska 1083, Prague, 14220, Czech.
SOURCE: Brain Research (1997), 769(2), 219-224
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have found earlier that the depolarization-induced release of acetylcholine from the brain could be inhibited by tacrine (tetrahydroaminoacridine) but the mechanism of this action of tacrine was not clarified (S. Tucek, V. Dolezal, J. Neurochem. 56 (1991) 1216). We have now investigated whether tacrine has an effect on the changes in the intracellular concentration of calcium ions ([Ca2+]i) induced by depolarization.
Expts. were performed on the cholinergic SN56 neuronal cell line with Fura-2 fluorescence technique of calcium imaging. The depolarization by 71 mmol/l K+ evoked min. increases of [Ca2+]i up to day 5 in culture. Then the response gradually increased and reached a plateau after 7 days in culture. A similar time course was observed for acetylcholinesterase activity. The effect of K+ ions was concentration-dependent and the concentration of 71
mmol/l K+ evoked maximum [Ca2+]i responses. The increases of [Ca2+]i did not
occur in the absence of extracellular calcium. They were mediated by high voltage-activated calcium channels of the L-type and the N-type. Nifedipine (2 μmol/l; L-type calcium channel blocker) and ω-conotoxin GVIA (100 nmol/l; N-type calcium channel blocker) diminished the response to 71 mmol/l K+ by 53% and 39%, resp., and their effects were additive (decrease to 8% of controls). Non-selective inorg. blocker of voltage-activated calcium channels LaCl3 (0.1 mmol/l) decreased the response by 83%. Tacrine attenuated the [Ca2+]i response in a concentration-dependent manner. At a concentration of 10 μmol/l it inhibited the
[Ca2+]i response by 55% and its inhibitory effect was additive with that of ω-conotoxin GVIA but not with that of nifedipine. An equimolar concentration of paraoxon, an irreversible inhibitor of cholinesterases, had no
influence on [Ca2+]i response. Tacrine exhibited the same inhibitory effect when paraoxon was present. In conclusion, our data indicate that high-voltage-activated calcium channels of the L-type and the N-type are both present in the SN56 cells but that they are fully expressed only after 6-7 days in culture. Tacrine attenuates the influx of calcium by inhibiting the L-type calcium channels. This inhibitory effect is not a consequence of the anticholinesterase activity of tacrine. The finding that low micromolar concns. of tacrine may interfere with calcium-dependent events is likely to be of importance for the evaluation of the therapeutic potential of the drug.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of tacrine on intracellular calcium in cholinergic SN56

L11 ANSWER 43 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
neuronal cells)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

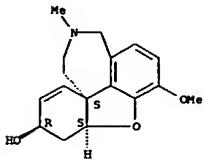
L11 ANSWER 44 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:561020 HCAPLUS
DOCUMENT NUMBER: 127:215107
TITLE: The effects of chronic tacrine therapy on d-tubocurarine blockade in the soleus and tibialis muscles of the rat
AUTHOR(S): Ibebunjo, Chikwendu; Donati, Francois; Fox, Gordon S.; Eshelby, Dayle; Tchervenkov, Jean I.
CORPORATE SOURCE: Department of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal, QC, Can.
SOURCE: Anesthesia & Analgesia (Baltimore) (1997), 85(2), 431-436
CODEN: AACRAT; ISSN: 0003-2999
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine (THA) is an anticholinesterase drug used to manage Alzheimer's dementia, but it is not clear how its chronic use might affect response to nondepolarizing muscle relaxants. We determined the magnitude and time course
of the effects of chronic oral THA and of i.v. THA on d-tubocurarine (dTC) blockade at the soleus and tibialis muscles. Six groups of adult rats were given 10 mg/kg THA twice daily by gavage for 1,2,4, or 8 wk (chronic THA groups), or 1 mL of saline twice daily by gavage for 1-8 wk (control), or i.v. THA approx. 20 min before (acute), and the cumulative dose-response curves of dTC at the tibialis and soleus muscles were determined
during indirect train-of-four stimulation in the anesthetized, mech. ventilated rat. The 50% ED (ED50) and 95% ED (ED95) of dTC in control rats were (mean) 30 and 61 μg/kg in the tibialis and 32 and 75 μg/kg in the soleus; resp. I.v. THA increased the ED95 of dTC 2.5- to 3-fold but did not alter the ED50. Chronic THA increased both the ED50 and ED95 of dTC 1.5- to 2-fold, and this effect tended to decrease with duration of THA therapy. We conclude that chronic THA therapy in rats causes resistance to dTC, with a tendency for the resistance to decrease with time, probably because of down-regulation of postsynaptic acetylcholine receptors. The same may apply to Alzheimer's patients taking THA chronically.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of chronic tacrine therapy on d-tubocurarine blockade in the soleus and tibialis muscles of the rat)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



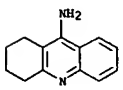
L11 ANSWER 45 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:529293 HCAPLUS
DOCUMENT NUMBER: 127:172349
TITLE: Novel molecular targets in the central nervous system for the actions of cholinesterase inhibitors: alterations of modulatory processes
AUTHOR(S): Rocha, E. S.; Pereira, E. F. R.; Swanson, K. L.; Albuquerque, E. X.
CORPORATE SOURCE: Department Pharmacology Experimental Therapeutics, University Maryland School Medicine, Baltimore, MD, 21201, USA
SOURCE: Medical Defense Bioscience Review, Proceedings, Baltimore, May 12-16, 1996 (1996), Volume 3, 1635-1643. National Technical Information Service: Springfield, Va.
CODEN: 64UTAN
DOCUMENT TYPE: Conference
LANGUAGE: English
AB To explore the effects of organophosphorus compds. on non-cholinergic systems in the CNS, the effects of soman, VX and paraoxon on cultured hippocampal neurons of the rat were studied using the patch-clamp technique to monitor release of excitatory and inhibitory transmitters and the function of several excitatory and inhibitory postsynaptic receptors. The authors provide evidence that VX at a concentration as low as 10 nM and the organophosphorus compound paraoxon at a concentration as low as 300 nM increase transmitter release from hippocampal neurons by acting locally at pre-synaptic release sites, an action that was independent of acetylcholinesterase catalytic activity and cholinergic receptor function. VX was more potent and more efficacious than paraoxon, which also antagonized the response of several types of receptors to transmitter. In the absence of TTX, VX elicited postsynaptic activity compatible with bursts fo presynaptic depolarizing events. In addition, the cholinesterase inhibitor galanthamine, a compound structurally related to the carbamate physostigmine, was seen to potentiate the nicotinic response of hippocampal neurons to acetylcholine (ACh); this potentiation was mediated via a site on the nicotinic acetylcholine receptor (nAChR) distinct from the ACh-binding site.
IT 357-70-0, Galanthamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(novel mol. targets in the central nervous system for the actions of cholinesterase inhibitors - alterations of modulatory processes)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 45 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

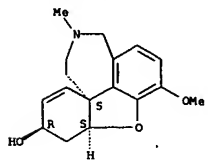


L11 ANSWER 46 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:472653 HCAPLUS
DOCUMENT NUMBER: 127:130426
TITLE: Influence of the CYP1A2 inhibitor fluvoxamine on tacrine pharmacokinetics in humans
AUTHOR(S): Becquemont, Laurent; Ragueneau, Isabelle; Le Bot, Marie Annick; Riche, Christian; Funck-Brentano, Christian; Jaillon, Patrice
CORPORATE SOURCE: Clinical Pharmacology Unit, Saint Antoine University Hospital, Paris, Fr.
SOURCE: Clinical Pharmacology and Therapeutics (St. Louis) (1997), 61(6), 619-627
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby-Year Book
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine is extensively metabolized by cytochrome P 4501A2 (CYP1A2). Fluvoxamine, a potent CYP1A2 inhibitor, may be coadministered with tacrine. The aim of this study was to examine the influence of fluvoxamine administration on the disposition kinetics of single-dose tacrine administration. Thirteen healthy volunteers participated in this double-blind, randomized crossover study, which compared the effects of fluvoxamine (100 mg/day during 6 days) and placebo on the pharmacokinetics of a single oral dose of tacrine (40 mg). Fluvoxamine caused a significant increase in tacrine area under the plasma concentration vs. time curve (AUC): arithmetic mean, 27 (95% confidence interval [CI], 19 to 38) ng·hr/mL vs. 224 (95% CI, 166 to 302) ng·hr/mL. Fluvoxamine caused a decrease in the apparent oral clearance of tacrine from 1683 to 200 L/h (mean), which was explained by a decrease in its nonrenal clearance. Five subjects had gastrointestinal side effects during fluvoxamine administration. Fluvoxamine administration was associated with significant increases in the plasma AUC values of three monohydroxylated tacrine metabolites and in the total urinary recovery measurements of tacrine and its metabolites (9.1% vs. 24.0% of recovery). These results may be attributable to fluvoxamine-dependent inhibition of CYP1A2, which is responsible of the biotransformation of tacrine into its monohydroxylated metabolites and further into dihydroxylated and reactive metabolites. Fluvoxamine inhibits the metabolism of tacrine. CYP1A2 may be the target of this inhibition. Fluvoxamine may modulate the hepatotoxicity of tacrine, depending on the relative contribution of tacrine and its reactive metabolites to this toxicity.
IT 321-64-2, Tacrine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(influence of cytochrome P 4501A2 inhibitor fluvoxamine on tacrine pharmacokinetics in humans)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 47 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:390113 HCAPLUS
DOCUMENT NUMBER: 127:75353
TITLE: Preclinical studies with galanthamine
AUTHOR(S): Mucke, Hermann A. M.
CORPORATE SOURCE: Waldheim Pharmazeutika GmbH, Vienna, A-1090, Austria
SOURCE: Drugs of Today (1997), 33(4), 259-264
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 52 refs. This chapter summarizes early investigations concerned with galanthamine hydrobromide, a well-tolerated morphine alkaloid with acetylcholine esterase inhibitor activity that has been exploited for a variety of clin. purposes in the past, and which is now being developed for Alzheimer's disease. The compound was first used by Bulgarian and Russian researchers in the 1950s, and much of the original literature of this time is, therefore, not easily accessible. Consistent with the contemporary practices, few safety and efficacy studies had been conducted before it was routinely used for postsurgery reversal of tubocurarine-induced muscle relaxation, muscular dystrophy and traumatic brain injury. As early as 1972, Soviet researchers had demonstrated that galanthamine could reverse scopolamine-induced amnesia in mice, a finding that was extended to man 4 yr later. However, this did not lead to the application of this compound in Alzheimer's disease until 1986, long after the cholinergic hypothesis of Alzheimer's disease had been first postulated. One of the reasons why galanthamine was not properly developed at this time is that it was available only in very limited amts. Although its chemical structure was known, and a laboratory-scale synthesis of very low yield had been developed by 1960, all supplies came from natural exts. until very recently.
IT 357-70-0, Galanthamine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. studies with galanthamine in treatment of Alzheimer's disease)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



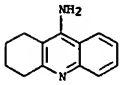
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 48 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:369147 HCAPLUS
DOCUMENT NUMBER: 127:44892
TITLE: Acetylcholinergic drugs. Their protective effects against glutamate-induced neuronal death in cerebral cortex and possible application to antidementia drugs
AUTHOR(S): Akaike, Akinori
CORPORATE SOURCE: Yakugakuku, Kyoto Daigaku, Kyoto, 606-01, Japan
SOURCE: Ikagaku Oyo Kenkyu Zaidan Kenkyu Hokoku (1996), Volume Date 1995, 14, 171-177
CODEN: IOKHEP; ISSN: 0914-5117
PUBLISHER: Ikagaku Oyo Kenkyu Zaidan
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Neuronal cells from 18-20 days old fetal rat cerebral cortex was used. Glutamate (GL)-induced neuronal death (ND) was inhibited by concomitant incubation with the N-methyl-D-aspartate (NMDA) receptor blocker MK-801 (1-10 μM). Short-term (10 min) exposure of NMDA induced ND in the Mg2+-free medium, but not in the normal medium. GL- and NMDA-induced ND was inhibited in the Ca2+-free medium. ND induced by non-NMDA receptor agonists was inhibited in the medium substituted Na+ with choline, but not in the Ca2+-free medium. Hb and Ne-nitro-L-arginine (NNA) inhibited GL- and NMDA-induced ND, but not kainic acid-induced ND. GL-induced ND in cells incubated for 24 h in the presence of 0.1-10 μM nicotine (Nic) was inhibited by Nic concentration-dependently. Preventive effect of nicotine on GL-induced ND was inhibited by hexamethonium, mecamylamine, and the α neuronal receptor antagonist α-bungarotoxin, but not atropine. Ionomycin-induced ND was inhibited by NNA and Hb, but not by MK-801. The acetylcholine (ACh) esterase inhibitor tacrine (100 μM) prevented GL-induced ND when added 24 h before GL treatment. These results suggest that acetylcholinergic drugs have the nicotinic receptor-mediated protective action against GL cytotoxicity in the cerebral cortex.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acetylcholinergic drugs. Their protective effects against glutamate-induced neuronal death in cerebral cortex and possible application to antidementia drugs)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

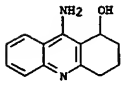


L11 ANSWER 49 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:329936 HCAPLUS
DOCUMENT NUMBER: 127:60155
TITLE: Metabolic disposition of the cognition activator tacrine in rats, dogs, and humans: species comparisons
AUTHOR(S): Pool, William F.; Reily, Michael D.; Bjorge, Susan M.; Woolf, Thomas F.
CORPORATE SOURCE: Dep. Pharmacokinetics Drug Metabolism, Parke Pharmaceutical Res., Warner-Lambert Co., Ann Arbor, MI, 48105, USA
SOURCE: Drug Metabolism and Disposition (1997), 25(5), 590-597
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The metabolic fate of tacrine [1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate (THA)] was examine in rats, dogs, and humans. After administration of single oral dose of [14C]THA to rats, dogs, and humans, drug-derived material was well absorbed, with urinary excretion being the predominant route of radiolabeled elimination. Metabolic profiling of plasma and urine from rats, dogs, and humans showed THA to be extensively metabolized with marked species differences in quant. amts. of metabolites observed Plasma were similar to resp. urinary profiles in all three species. Present in profiles of urine from rats were 1-hydroxy (OH)-THA (major), 2-OH-THA, and 4-OH-THA, and unchanged THA. Also observed were trace amts. of more polar metabolites, presumably arising from sequential metabolism Metabolic profiling of dog urine also showed 1-OH-THA to be the major metabolite, with trace amts. of the 2-OH-THA and 4-OH-THA regioisomers and THA excreted. In dog urine, more of the radioactivity was associated with polar metabolites, including 1,3-dihydroxy-THA and a dihydrodiol metabolite. Human urinary metabolic profiles were more similar to that in dogs than in rats, with no single metabolite constituting >10% of urinary radioactivity. Present in human urine were phenol glucuronide metabolites, of which 7-OH-THA was identified as an aglycon. Relevance of the marked quant. differences in THA metabolism between rats, dogs, and humans to species differences in THA hepatotoxic potential remains to be established.

IT 124027-47-0, 1-Hydroxy-tacrine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(comparison of metabolic disposition of cognition activator tacrine in rats, dogs, and humans)

RN 124027-47-0 HCAPLUS
CN 1-Acridinol, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS

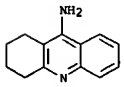
L11 ANSWER 49 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 50 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:177657 HCAPLUS
DOCUMENT NUMBER: 126:271745
TITLE: Tremulous jaw movements induced by the acetylcholinesterase inhibitor tacrine: effects of antiparkinsonian drugs
AUTHOR(S): Cousins, Michael S.; Carriero, Debbie L.; Salamone, John D.
CORPORATE SOURCE: Department of Psychology, University of Connecticut, Storrs, CT, 06269-1020, USA
SOURCE: European Journal of Pharmacology (1997), 322(2/3), 137-145
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

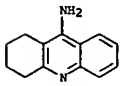
AB Several expts. were conducted to study the effects of established or potential antiparkinsonian drugs on the tremulous jaw movements induced by the anticholinesterase tacrine (9-amino-1,2,3,4-tetrahydroaminoacridine hydrochloride). In the first group of four expts., sep. groups of animals that received 2.5 or 5.0 mg/kg tacrine showed a dose-dependent decrease in tremulous jaw movements following co-administration of the non-selective dopamine receptor agonist apomorphine, the full dopamine D2 receptor agonist bromocriptine, and the full dopamine D1 receptor agonist APB (R(+)-6-bromo-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine). Co-administration of the partial dopamine D1 receptor agonist SKF 38393 (R(+)-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-benzazepine; 7.5-30.0 mg/kg) did not reduce tremulous jaw movements produced by 2.5 or 5.0 mg/kg tacrine. In animals treated with 2.5 mg/kg tacrine, co-administration of SKF 38393 resulted in a dose-related trend towards a potentiation of tremulous jaw movements. In the second group of expts., all rats received 2.5 mg/kg tacrine. The dopamine precursor L-DOPA (L-3,4-dihydroxyphenylalanine), the dopamine and norepinephrine releasing agent amantadine, and the muscarinic receptor antagonist benztropine all reduced tremulous jaw movements induced by 2.5 mg/kg tacrine. Across all expts., it was noted that apomorphine, bromocriptine and benztropine were more potent than amantadine and L-DOPA. These results are broadly consistent with the therapeutic doses of these agents noted in the clin. literature. The results of these expts. indicate that tremulous jaw movements in rats may be a useful model for evaluating potential antiparkinsonian agents.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tacrine-induced tremulous jaw movement as model for evaluating antiparkinsonian agents)

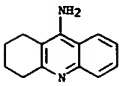
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



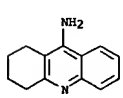
L11 ANSWER 51 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:171638 HCAPLUS
DOCUMENT NUMBER: 126:220612
TITLE: Tacrine interacts with an allosteric activator site on α4β2 nAChRs in M10 cells
AUTHOR(S): Svensson, Anne-Lie; Nordberg, Agneta
CORPORATE SOURCE: Department of Clinical Neuroscience and Family Medicine, Division of Nicotine Research, Huddinge University Hospital, Huddinge, S-141 86, Swed.
SOURCE: NeuroReport (1996), 7(13), 2201-2205
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of chronic treatment with the cholinesterase inhibitor tacrine on α4β2 nicotinic acetylcholine receptors (nAChRs) was investigated in a transfected fibroblast cell line, M10. Tacrine significantly increased (+46%; 5 + 10-8 to 10-5 M) and decreased (-74%; 2+10-5 to 10-4 M) the number of nAChRs in the M10 cells in a concentration-dependent manner when using [3H]cytisine as labeled ligand. The mRNA levels for α4 or β2 nAChR subunits remained unchanged following the treatment. The tacrine-induced increase in number of nAChRs was significantly blocked by the antagonist mecamylamine (10-4 M), while tubocurarine (10-4 M) had no effect. Neither of the antagonists prevented the decrease in the number of nAChRs obtained at the higher concentration of tacrine. Similar to nicotine, tacrine (5+10-5 M) decreased the turnover rate of nAChRs, which might indicate neuroprotective properties. This study demonstrates that tacrine interacts with two sites on nAChRs, where activation of the non-competitive allosteric site might contribute to the clin. efficacy of tacrine treatment in AD patients.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tacrine effect on fibroblast α4β2 nicotinic acetylcholine receptors in relation to neuroprotective activity in Alzheimer disease)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



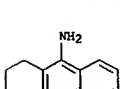
L11 ANSWER 52 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:169284 HCAPLUS
DOCUMENT NUMBER: 126:233529
TITLE: SA4503, a novel cognitive enhancer, with σ1 receptor agonistic properties
AUTHOR(S): Matsuno, Kiyoshi; Senda, Toshihiko; Kobayashi, Tetsuya; Okamoto, Kazuyoshi; Nakata, katsuhiko; Mita, Shiro
CORPORATE SOURCE: Cent. Res. Labs., Santen Pharmaceutical Co., Ltd., Osaka, 533, Japan
SOURCE: Behavioural Brain Research (1997), 83(1/2), 221-224
CODEN: BBREDI; ISSN: 0166-4328
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We found a potent and selective sigma1 (σ1) receptor ligand, SA4503 (1-(3,4-dimethoxypheneethyl)-4-(3-phenylpropyl)piperazine dihydrochloride). This compound had a high affinity for σ1 receptor subtype (IC50 = 17 ± 1.9 nM), but a low affinity for σ2 receptor subtype (EC50 = 1800 ± 310 nM). The present study examines the effect of this compound on the central cholinergic functions, since σ receptor has been reported to interact with the central cholinergic neurons. SA4503 elicited the increase in extracellular acetylcholine level in rat frontal cortex, while it did not affect the stratal acetylcholine level. On the other hand, tetrahydroaminoacridine (THA), an acetylcholinesterase (AChE) inhibitor, increased the extracellular acetylcholine level in both regions. Although both compds. had anti-amnesic effect against scopolamine-induced memory impairment, THA also induced catalepsy in rats. These results suggest that SA4503 may be a novel cognitive enhancer, with σ1 receptor agonistic properties. In addition, SA4503 does not cause striatal cholinomimetic side-effects, which is different from THA.
IT 321-64-2
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(SA4503, a novel cognitive enhancer, with σ1 receptor agonistic properties)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



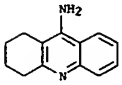
L11 ANSWER 53 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:144863 HCAPLUS
DOCUMENT NUMBER: 126:312592
TITLE: Nicotinic acetylcholine receptor (nACh-R) agonist-induced changes in brain monoamine turnover in mice
AUTHOR(S): Tani, Yoshihiro; Saito, Kyoshi; Tsuneyoshi, Atsuko; Imoto, Masahiro; Ohno, Tomochika
CORPORATE SOURCE: Suntory Institute for Biomedical Research, Osaka, 618, Japan
SOURCE: Psychopharmacology (Berlin) (1997), 129(3), 225-232
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects were evaluated of nicotinic acetylcholine receptor (nACh-R) agonists such as (-)-nicotine and related compds. on brain monoamine turnover. A single administration of (-)-nicotine increased noradrenaline (NA) and dopamine (DA) turnover dose-dependent, and the maximum effects were achieved 30 min after treatment with (-)-nicotine (1.0 mg/kg). Serotonin (5-HT) turnover was increased at a low dose of (-)-nicotine (0.04 mg/kg) but decreased at a high dose (1.0 mg/kg). The (-)-nicotine (1.0 mg/kg)-induced changes in monoamine turnover were blocked by pretreatment with the centrally acting nACh-R channel blocker mecamylamine (2.0 mg/kg IP) but not by hexamethonium (2.0 mg/kg IP). Systemically administered (-)-nicotine can enhance brain NA and DA turnover and affect 5-HT turnover, both of which are mediated by central nACh-R. The changes in the monoamine turnover induced by (±)-anabasine were similar to those induced by (-)nicotine, while (-)-lobeline and (-)-cytisine had little effect, and 1,1-dimethyl-4-phenyl-piperazinium (DMPP) increased NA and 5-HT turnover but not DA turnover at all doses tested. (S)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole (ABT-418), a selective neuronal nACh-R agonist, increased NA, DA, and 5-HT turnover, but had a weaker effect on DA turnover than NA and 5-HT turnover. 9-Amino-1,2,3,4-tetrahydroacridine (THA) increased monoamine turnover in the brain. Pretreatment with mecamylamine completely blocked the THA-induced increase in NA and 5-HT turnover. (-)-Cytisine completely inhibited the nACh-R agonist- and THA-induced increases in NA turnover, and normalized the changes in 5-HT turnover.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(induced changes in brain monoamine turnover)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 54 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:137492 HCAPLUS
DOCUMENT NUMBER: 126:233476
TITLE: Tremulous jaw movements produced by acute tacrine administration: possible relation to parkinsonian side effects
AUTHOR(S): Mayorga, A. J.; Carriero, D. L.; Cousins, M. S.; Gianutsos, G.; Salamone, J. D.
CORPORATE SOURCE: Departments of Psychology and Pharmaceutical Sciences, University of Connecticut, Storrs, CT, 06269-1020, USA
SOURCE: Pharmacology, Biochemistry and Behavior (1997), 56(2), 273-279
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous work has shown that cholinomimetic drugs induce "vacuous" or non-directed jaw movements in rats. In the present study, five expts. were conducted to provide a pharmacol., anatomical and behavioral characterization of tacrine-induced vacuous jaw movements. In the first experiment, tacrine produced vacuous chewing in a dose-related manner in a range of 1.25 mg/kg to 1.0 mg/kg. This effect was reduced, also in a dose-related manner, by the co-administration of the muscarinic antagonist scopolamine in a range of 0.125 to 1.0 mg/kg, but not by N-methylscopolamine. The fourth experiment examined the effect of scopolamine (2.5 to 10.0 μg) injected into the ventrolateral striatum on vacuous jaw movements induced by 5.0 mg/kg tacrine. Intrastriatal injections of scopolamine completely blocked tacrine-induced jaw movements. The fifth experiment utilized a slow-motion videotaping system to analyze the temporal characteristics of vacuous chewing induced by 5.0 mg/kg tacrine. The vast majority of the movements occurred in rapid "bursts," and anal. of interresponse times (i.e., the between each jaw movement) showed that most of the jaw movements occurred within a local frequency range of 3 to 7 Hz. Thus, tacrine-induced jaw movements are reduced by antimuscarinic treatment, and most of these movements occur in the parkinsonian tremor frequency range. Tremulous jaw movements induced by tacrine in rats appear to share some characteristics with Parkinsonian tremor.
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(tremulous jaw movements produced by acute tacrine administration and possible relation to parkinsonian side effects)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

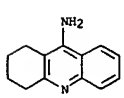


L11 ANSWER 55 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:79865 HCAPLUS
DOCUMENT NUMBER: 126:180637
TITLE: The tolerability and safety profile of tacrine
AUTHOR(S): Pendlebury, William W.; Solomon, Paul R.
CORPORATE SOURCE: Department of Pathology, University of Vermont, Burlington, VT, 05405, USA
SOURCE: Reviews in Contemporary Pharmacotherapy (1995), 6(7), 349-357
CODEN: RCPHFW; ISSN: 0954-8602
PUBLISHER: Marius Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.27 refs. Tacrine is a potent, centrally acting, acetylcholinesterase inhibitor that has been approved for the treatment of Alzheimer's disease in several countries throughout the world, including the USA, France and Australia. The scientific rationale for the use of tacrine is based on the known acetylcholine deficit that develops early, and persists, in Alzheimer's disease, and is due to a loss of cholinergic neurons in the basal forebrain region. The theor. mechanism of action of tacrine is to increase the longevity of acetylcholine mols. in cholinergic synapses by reversibly blocking the activity of acetylcholinesterase. Tacrine is not thought to retard the ongoing neuronal degeneration in the basal forebrain region, and thus would be expected to have limited efficacy over time. In the USA, approval of tacrine was based on two, well-controlled multi-center trials that demonstrated efficacy, as measured by both an objective neuropsychol. instrument and a clin.-based instrument. In addition, input from care givers indicated improved performance in activities of daily living. In the most recent trial, efficacy persisted over a 30-wk time interval. In all large scale multi-center studies, tacrine was safe and well tolerated. The most significant adverse events reported with tacrine were time-dependent hepatoxicity, and dose-dependent cholinergic gastrointestinal side effects. The former were managed with regular monitoring of serum alanine aminotransferase, with reversion to normal of all enzyme abnormalities with cessation of tacrine. The latter have been more difficult to manage, but gastrointestinal side effects have responded to dose reduction and slowed dose titration
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tolerability and safety profile of tacrine in humans)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 55 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

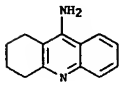
L11 ANSWER 56 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:79864 HCAPLUS
DOCUMENT NUMBER: 126:166413
TITLE: The clinical efficacy of tacrine
AUTHOR(S): Harvey, Richard J.; Eagger, Sarah A.
CORPORATE SOURCE: Dementia Research Group, St Mary's Hospital Medical School and The National Hospital for Neurology and Neurosurgery, London, WC1N 3BG, UK
SOURCE: Reviews in Contemporary Pharmacotherapy (1995), 6(7), 335-348
CODEN: RCPHFW; ISSN: 0954-8602
PUBLISHER: Marius Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine (1,2,3,4-tetrahydro-9-aminoacridine), THA, Cognex, a cholinesterase inhibitor, has become the first licensed treatment for Alzheimer's disease. Its variety of pharmacol. properties include inhibition of acetylcholinesterase and butyrylcholinesterase, action on muscarinic and nicotinic receptors, and on sodium, potassium and calcium channels, and the ability to affect the uptake, synthesis and release of a range of neurotransmitters. In vivo it has the ability to modulate amyloid precursor protein secretion. Based upon its potent inhibition of acetylcholinesterase and the cholinergic hypothesis of Alzheimer's disease (AD), it has been extensively studied as a possible treatment for AD. Early trials in AD patients suffered from design and methodol. flaws resulting in mixed results. More recent studies, designed since FDA guidelines on anti-dementia drug trials were published, have consistently shown a significant advantage of tacrine over placebo on both cognitive tests and on observations made by clinicians and carers. However, the response to tacrine is variable, with only 20-30% of patients showing a significant response, and up to half of patients withdrawing from trials due to adverse events, predominantly cholinergic side effects and elevation of liver transaminases. Techniques including developments of psychometric testing, orthostatic blood pressure, functional imaging and quant. EEG recording have been used to monitor treatment and predict response. Tacrine offers significant benefits to a subgroup of AD sufferers, with effects that are probably long term and which possibly modulate the course of the disease. Tacrine is likely to be the first cholinesterase inhibitor in what has become a new approach to the treatment of AD.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. efficacy of tacrine in humans)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



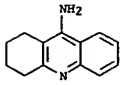
REFERENCE COUNT: 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 56 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 57 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:43910 HCAPLUS
DOCUMENT NUMBER: 126:152679
TITLE: Tacrine inhibits nicotinic secretory and current responses in adrenal chromaffin cells
AUTHOR(S): Sugawara, Takeshi; Ohta, Toshio; Asano, Tadashi; Ito, Shigeo; Nakazato, Yoshikazu
CORPORATE SOURCE: Laboratory of Pharmacology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, 060, Japan
SOURCE: European Journal of Pharmacology (1997), 319(1), 123-130
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine enhanced acetylcholine-induced catecholamine secretion with a concentration of ≤10 μM, but inhibited it at over 10 μM in perfused adrenal glands. Qual. the same result was obtained with physostigmine. Both tacrine and physostigmine only inhibited the secretory responses to carbachol and/or nicotine in perfused glands and dispersed chromaffin cells. Acetylcholinesterase activity of adrenal homogenates was inhibited by tacrine and physostigmine in a concentration-dependent manner. In whole-cell patch-clamp expts., tacrine and physostigmine caused reversible inhibition of nicotine-evoked inward currents with a dose range similar to that for the inhibitory action on the secretory response. These results suggest that the enhancing effect of tacrine and physostigmine on acetylcholine-induced catecholamine secretion results from the prevention of enzymic hydrolysis of acetylcholine in adrenal glands and that the inhibitory effect is due to the inhibition of nicotinic receptor-mediated membrane currents in adrenal chromaffin cells.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tacrine and physostigmine inhibit nicotinic secretory and current responses in adrenal chromaffin cells at high concns. and inhibit acetylcholine-induced catecholamine secretion due to acetylcholinesterase inhibition)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

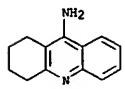


L11 ANSWER 58 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:27889 HCAPLUS
DOCUMENT NUMBER: 126:126802
TITLE: Cognitive effects of nicotinic cholinergic receptor agonists in non-human primates
AUTHOR(S): Buccafusco, J. J.; Prendergast, M. A.; Terry, A. V., Jr.; Jackson, W. J.
CORPORATE SOURCE: Alzheimer's Res. Center, Med. College Georgia, Augusta, GA, 30912-2300, USA
SOURCE: Drug Development Research (1996), 38(3-4), 196-203
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The centrally acting cholinesterase inhibitor tacrine was compared with three nicotinic acetylcholine receptor (nAChR) agonists for their abilities to enhance performance of mature adult macaques performing a computer-automated version of the delayed matching-to-sample (DMTS) task. All four drugs enhanced DMTS performance at one or more doses, although ABT-418 [(S)-3-methyl-5-(1-methyl-2-pyrrolidinyl) isoxazole] may be the most potent and the most effective of the four. Nicotine was less potent and less effective than ABT-418 but was more potent than either tacrine or isoarecolone. At each animal's resp. maximally ED, task improvement ranged from approx. 14 to 30% over vehicle performance levels. Despite the significantly enhanced levels of performance improvement obtained on the day of drug administration, when the animals were tested 24 h later (in the absence of drug), only nicotine-treated animals exhibited a significant improvement in performance. In an attempt to help explain this protracted improvement in DMTS performance to nicotine, cell surface nerve growth factor (NGF) receptors were measured in cultured PC-12 cells before and after exposure to nicotine. Exposure to nicotine for 24 h resulted in a significant increase in cell surface NGF in the cells. However, even after nicotine was removed from the culture medium, NGF receptor protein continued to increase for an addnl. 24 h. The results of this study are consistent with the possibility that stimulation of central nAChRs may be employed to improve cognitive function in cognitively impaired individuals. They also suggest that one potential mechanism for the protracted beneficial effect of nicotine may involve the enhanced expression of brain NGF receptors.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cognitive effects of nicotinic agonists compared to cholinesterase inhibitor in non-human primates)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 58 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

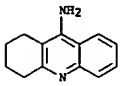
L11 ANSWER 59 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:6403 HCAPLUS
DOCUMENT NUMBER: 126:84106
TITLE: Overlapping drug interaction sites of human butyrylcholinesterase dissected by site-directed mutagenesis
AUTHOR(S): Loewenstein-Lichtenstein, Yael; Glick, David; Gluzman, Nelly; Sternfeld, Meira; Zakut, Haim; Soreq, Hermona
CORPORATE SOURCE: Inst. Life Sciences, Hebrew Univ. Jerusalem, Jerusalem, 91904, Israel
SOURCE: Molecular Pharmacology (1996), 50(6), 1423-1431
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Butyrylcholinesterase [BuChE (acylcholine acyl hydrolase); EC 3.1.1.8] limits the access of drugs, including tacrine, to other proteins. The "atypical" BuChE variant, in which Asp70 at the rim of the active site gorge is substituted by glycine, displayed a more drastically weakened interaction with tacrine than with cocaine, dibucaine, succinylcholine, BW284c51 [1,5-bis(4-allyldimethylammoniumphenyl)pentan-3-one dibromide], or α-solanine. To delineate the protein domains that are responsible for this phenomenon, we mutated residues within the rim of the active site gorge, the region parallel to the peripheral site in the homologous enzyme acetylcholinesterase [AChE (acetylcholine acetyl hydrolase); EC 3.1.1.7], the oxyanion hole, and the choline-binding site. When expressed in microinjected Xenopus laevis oocytes, all mutant DNAs yielded comparable amts. of immunoreactive protein products. Most mutants retained catalytic activity close to that of wild-type BuChE and were capable of binding ligands. However, certain modifications in and around the oxyanion hole caused a dramatic loss in activity. The affinities for tacrine were reduced more dramatically than for all other ligands, including cocaine, in both oxyanion hole and choline-binding site mutants. Modified ligand affinities further demonstrated a peripheral site in residues homologous with those of AChE. BuChE mutations that prevented tacrine interactions also hampered its ability to bind other drugs and inhibitors, which suggests a partial overlap of the binding sites. This predicts that in addition to their genetic predisposition to adverse responses to tacrine, homozygous carriers of "atypical" BuChE will be overly sensitive to addnl. anticholinesterases an especially so when exposed to several anticholinesterases in combination.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(overlapping drug interaction sites of human butyrylcholinesterase dissected by site-directed mutagenesis)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 60 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:760270 HCAPLUS
DOCUMENT NUMBER: 126:42578
TITLE: The nature of the inhibition of camel retina acetylcholinesterase (EC 3.1.1.7) activity by tetrahydroaminoacridine
AUTHOR(S): Al-Jafari, Abdulaziz A.
CORPORATE SOURCE: Dept. of Biochemistry, King Saud Univ., Riyadh, Saudi Arabia
SOURCE: Journal of Ocular Pharmacology and Therapeutics (1996), 12(4), 503-514
CODEN: JOPTFU; ISSN: 1080-7683
PUBLISHER: Liebert
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of the inhibition of camel (Camelus dromedarius) retina acetylcholinesterase (AChE) activity by tetrahydroaminoacridine (THA, tacrine) was investigated. The nonsignificant change of the percent inhibition of AChE by THA with respect to various lengths of the preincubation period indicated a reversible type of inhibition. THA reversibly inhibited AChE activity in a concentration-dependent manner; the IC50 was 0.23 μM and the IC100 was 14.22 μM. The Km for the hydrolysis of acetylthiocholine iodide by AChE was 62.6 μM in the absence of THA; the value increased in the THA-containing systems. The Vmax was 0.472 μmole/min/mg protein in the absence of THA and decreased in the presence of THA. Dixon, as well as Lineweaver-Burke, plots and their secondary replots indicated that the nature of the inhibition was of the linear mixed type, which is considered to be a combination of partial competitive and pure noncompetitive inhibitions. The values of Ki(slope) and K'i(intercept) were estimated as 0.068 μM and 0.181 μM, resp. The K'i was greater than Ki, indicating that THA has a greater affinity of binding at the peripheral site than the active site of camel retina AChE. The use of camel retina as an exptl. animal model may open new avenues for studying acetylcholine and AChE metabolism

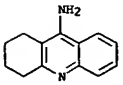
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acetylcholinesterase of camel retina inhibition by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 61 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:756021 HCAPLUS
DOCUMENT NUMBER: 126:84966
TITLE: Allosteric regulation of the binding of [3H] acetylcholine to m2 muscarinic receptors
AUTHOR(S): Gnagey, Ann; Ellis, John
CORPORATE SOURCE: Department Psychiatry, Univ. Vermont, Burlington, VT, 05405, USA
SOURCE: Biochemical Pharmacology (1996), 52(11), 1767-1775
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Muscarinic receptors of the m2 subtype expressed in Chinese hamster ovary cells were labeled with [methyl-3H]acetylcholine ([3H]ACh), and the rate of dissociation in the presence and absence of several compds. known to exert allosteric effects on labeled antagonist binding was observed At 25°, [3H]ACh bound to the receptors with a Kd of 1.2 nM and dissociated with a half-time of 1.6 min. This binding was sensitive to appropriate concns. of guanine nucleotide and the muscarinic antagonist N-methylscopolamine (NMS). Gallamine, tetrahydroaminoaminoacridine, physostigmine, obidoxime, and 3,4,5-trimethoxybenzoic acid 8-(diethylamino)octyl ester (TMB-8) all inhibited the binding of [3H]ACh and all slowed the rate of dissociation of [3H]ACh in a concentration-dependent manner. However, the nature of some of the allosteric effects differed from previous studies that used other labeled ligands. In particular, TMB-8, which is very effective in slowing the dissociation of the antagonist [3H]NMS, had much weaker effects on the dissociation of [3H]ACh. Furthermore, TMB-8 was able to partially reverse the stronger effects of gallamine on the dissociation of [3H]ACh, consistent with the possibility that TMB-8 and gallamine share a common site on the receptor. In summary, the binding of ACh to muscarinic receptors is subject to allosteric regulation, and assays using [3H]ACh may be especially useful in the evaluation of potential allosteric regulators of muscarinic systems.

IT 321-64-2, THA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(allosteric regulation of acetylcholine binding to m2 muscarinic receptors)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

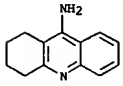


L11 ANSWER 61 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 62 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:711988 HCAPLUS
DOCUMENT NUMBER: 126:26679
TITLE: Inhibition of histamine versus acetylcholine metabolism as a mechanism of tacrine activity
AUTHOR(S): Morisset, Severine; Traiffort, Elisabeth; Schwartz, Jean-Charles
CORPORATE SOURCE: Unite de Neurobiologie et Pharmacologie (U. 109) de l'INSERM, Centre Paul Broca, 2ter rue d'Alesia, Paris, 75014, Fr.
SOURCE: European Journal of Pharmacology (1996), 315(1), R1-R2
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Following tacrine administration i.p. to mice, the histamine N-methyltransferase activity of brain homogenates was more potently inhibited than the acetylcholinesterase activity (ID50 of 5.3 mg/kg vs. 13.6 mg/kg). The formation of the metabolite, tele-methylhistamine, in brain of mice treated with an histamine H3 receptor antagonist was abolished by tacrine with an ID50 as low as 1.2 mg/kg. The participation of histamine in the actions of tacrine and the relevance of histamine H3 receptor antagonists in Alzheimer's disease are suggested.

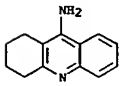
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of histamine vs. acetylcholine metabolism as a mechanism of Alzheimer's disease therapy with tacrine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 63 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:620335 HCAPLUS
DOCUMENT NUMBER: 125:265023
TITLE: The rationale for E2020 as a potent acetylcholinesterase inhibitor
AUTHOR(S): Kawakami, Yoshiyuki; Inoue, Atsushi; Kawai, Takatoshi; Wakita, Misako; Sugimoto, Hachiro; Hopfinger, Anton J.
CORPORATE SOURCE: Tsukuba Res. Lab., Eisai Co., Ltd., Ibaraki, 300-26, Japan
SOURCE: Bioorganic & Medicinal Chemistry (1996), 4(9), 1429-1446
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The phase III drug-candidate, E2020, developed for treatment of Alzheimer's, and possibly other dementias, and its analogs have been the focus of extensive mol. pharmacol. and structural studies. The potency and selectivity of E2020 as an inhibitor of acetylcholinesterase, AChE, in the brain is established. A combination of mol. modeling and QSAR studies have been used throughout the evolution of the AChE inhibitor program leading to the benzylpiperidine series, and, ultimately, E2020. QSAR studies have identified requirements to optimize inhibition activity as a function of substituent choice on both the indanone and benzyl rings in the E2020 class inhibitors. A combination of x-ray crystal structure studies of E2020 isomers and the mol. shape anal., MSA, of E2020 and its analogs has led to a postulated active conformation, and mol. shape, for these AChE inhibitors. The active mol. shape corresponds to a high degree of shape similarity between the two E2020 isomers which, in turn, is consistent with the observed high inhibition potencies of both of these compds. Intermol. docking studies were carried out for E2020 and some analogs with the crystal structure of AChE when it became available. The docking simulations involving E2020 analogs suggest these inhibitors do not bind at the acetyl-binding geometries are consistent with the postulated active conformations derived from structure-activity (receptor geometry independent) information.

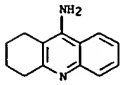
IT 321-64-2, THA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(E2020 as potent acetylcholinesterase inhibitor)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 64 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:601100 HCAPLUS
DOCUMENT NUMBER: 125:267734
TITLE: Evaluation of the therapeutic efficacy of some antimuscarinics against soman in vivo
AUTHOR(S): Lau, Wai-Man; Lewis, Katie J.; Dawson, Raymond M.
CORPORATE SOURCE: Aeronautical Maritime Res. Lab., Defence Sci. Technol. Organization, Melbourne, 3001, Australia
SOURCE: Journal of Applied Toxicology (1996), 16(5), 423-430
CODEN: JJATDK; ISSN: 0260-437X
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The therapeutic efficacy of tacrine, atropine and glycopyrrolate alone or in combination with the oxime HI-6 against soman was evaluated in anesthetized rats. Arterial blood pressure, heart rate, respiratory frequency and body temperature were monitored in vivo. Blood cholinesterases were determined after each drug or soman challenge. At the lowest concentration tested (2.5 mg kg-1), tacrine was effective in improving the survivability of the rat by a factor of 2.6 (protection ratio), whereas the protection by atropine or glycopyrrolate was either insignificant or only marginally effective (protection ratio range from 1.0 to 1.9). In combination with HI-6, atropine increased the ratio to 4.6. In contrast, tacrine with HI-6 failed to improve the efficacy of the regimen, while glycopyrrolate plus HI-6 showed only slight improvement. The four physiol. parameters monitored were relatively constant during the time course of the experiment in both the control and those with drug therapy. The more noticeable changes occurred toward the end of the experiment when sufficient amount of soman was injected to cause lethality. Death of the animal was usually preceded by a surge of arterial blood pressure and heart rate and a decrease in respiratory frequency. These physiol. parameters rapidly deteriorated to zero just before the animal die. Blood and plasma cholinesterase were significantly inhibited after the animal received a relatively small dose of soman (20 μg kg-1) and were almost completely inactivated after the LD of soman was administered. However, these changes of enzyme activity did not correspond well with the survivability of the rat. The inclusion of HI-6 with the three antimuscarinics appeared to be capable of protecting some cholinesterase against soman.

IT 321-64-2, Tacrine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic efficacy of antimuscarinics against soman in vivo)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

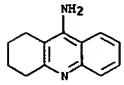


L11 ANSWER 64 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 65 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:515765 HCAPLUS
DOCUMENT NUMBER: 125:185385
TITLE: Blockade of cardiac nicotinic responses by anticholinesterases
AUTHOR(S): Paddle, Brian M.; Dowling, Margaret H.
CORPORATE SOURCE: Department Defence, Aeronautical Maritime Research Laboratory, Melbourne, 3001, Australia
SOURCE: General Pharmacology (1996), 27(5), 861-872
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tacrine (10 μM) and physostigmine (10 μM) completely inhibited the pos. chronotropic and inotropic actions of acetylcholine (Ach) or nicotine in the atropinized guinea pig right atria. Edrophonium (6 μM) and soman (0.1 μM) completely inhibited these nicotinic responses, as well as the associated increase in pyridine nucleotide fluorescence and vasodilation induced by ACh in the atropinized guinea pig perfused heart. The 200-fold increase in noradrenaline release induced by ACh in the perfused heart was blocked by 10 μM tacrine and 6 μM edrophonium. Tacrine (10 μM) reduced the basal heart rate of both prepns. Edrophonium (6 μM) induced a 5-6-fold increase in basal 3,4-dihydroxyphenylethylene glycol release. The inhibition of nicotinic receptor activation in the atria by the anticholinesterases appeared to be mainly noncompetitive. IC50 values ranged 0.1-10 μM in the perfused heart and 1-100 μM in atria (in either case tacrine about 2 μM). The possibility that these compds. have a direct action at nicotinic receptors is discussed.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nicotinic receptors of heart blockade by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

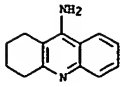


L11 ANSWER 66 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:478108 HCAPLUS
DOCUMENT NUMBER: 125:158423
TITLE: α2-Adrenoceptor antagonists potentiate acetylcholinesterase inhibitor effects on passive avoidance learning in the rat
AUTHOR(S): Camacho, Fernando; Smith, Craig P.; Vargas, Hugo M.; Winslow, James T.
CORPORATE SOURCE: Neuroscience Therapeutic Domain, Somerville, NJ, 08876-1258, USA
SOURCE: Psychopharmacology (Berlin) (1996), 124(4), 347-354
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cholinergic hypothesis of Alzheimer's disease (AD) has strongly influenced research on learning and memory over the last decade. However, there has been limited success treating AD dementia with cholinomimetics. Furthermore, there are indications that other neurotransmitter systems affected by this disease may be involved in cognitive processes. Animal studies have suggested that norepinephrine and acetylcholine may interact in learning and memory. The current expts. investigate this interaction in a step-down passive avoidance paradigm after coadministration of acetylcholinesterase inhibitors and α2-adrenoceptor antagonists. Administration of acetylcholinesterase inhibitors heptylphysostigmine (0.625-5.0 mg/kg, i.p.), tacrine (2.5-10.0 mg/kg, orally), velnacrine (0.312-2.5 mg/kg, s.c.), and galanthamine (0.312-2.5 mg/kg, i.p.) each enhanced retention of a passive avoidance response at selected moderate doses administered 30-60 min prior to training. The α2-adrenoceptor antagonists idazoxan (0.312-2.5 mg/kg, i.p.), yohimbine (.078-0.312 mg/kg, i.p.) and P 867480 (0.156-0.625 mg/kg, i.p.) alone failed to enhance learning in this paradigm. Coadministration of a subthreshold dose of heptylphysostigmine (0.625 mg/kg, i.p.) with doses of idazoxan, yohimbine or P 867480 enhanced passive avoidance learning. This synergistic interaction may represent effects of antagonism of presynaptic α2-adrenoceptor since coadministration of heptylphysostigmine and the selective postsynaptic α2-adrenoceptor antagonist SKF 104856 did not result in enhanced learning. Taken together these data suggest noradrenergic activation through pre-synaptic α2-adrenoceptor blockade may potentiate cholinergic activity in the formation of a long-term memory trace. These observation may have implications for the treatment of AD with cholinergic and adrenergic agents.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(α2-adrenoceptor antagonists potentiate acetylcholinesterase inhibitor effects on passive avoidance learning in rats)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

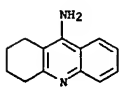
L11 ANSWER 66 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 67 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:456793 HCAPLUS
DOCUMENT NUMBER: 125:158356
TITLE: Differential effect of tacrine and physostigmine on the secretion of the β-amyloid precursor protein in cell lines
AUTHOR(S): Lahiri, Debomoy K.; Farlow, Martin R.
CORPORATE SOURCE: Lab. Molecular Neurogenetics, Indiana Univ. Sch. Med., Indianapolis, IN, 46202, USA
SOURCE: Journal of Molecular Neuroscience (1996), 7(1), 41-49
CODEN: JMNEES; ISSN: 0895-8696
PUBLISHER: Humana
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The senile plaque in Alzheimer's disease (AD) consists mainly of the amyloid β-peptide (Aβ) derived from a family of large integral membrane glycoproteins, beta-amyloid precursor proteins (βAPP). Soluble derivs. of βAPP generated by the proteolytic processing of full-length βAPP are normally secreted into the conditioned medium of cultured cells. Here we have investigated the possibility that the processing of βAPP can be regulated by the cholinesterase inhibitors physostigimine and tacrine. Both drugs mildly improve cognitive functions in some patients with AD. We analyzed the level of βAPP in glial, neuroblastoma, and pheochromocytoma cells by immunoblotting cell lysates and conditioned media using a monoclonal antibody, MAb22C11. The levels of soluble βAPP derivs. normally present in conditioned media was severely inhibited by treating cells with tacrine but not with physostigimine. Whereas the treatment of cells with tacrine resulted in a small decrease in the intracellular levels of βAPP, treating cells with physostigimine resulted in a slight increase in the intracellular levels of βAPP compared to untreated cells. The effect of tacrine on the secretion of βAPP was not affected by cotreating cells with muscarinic agents, staurosporine, or the calcium ionophore. Our results suggest that a decrease in the secretion of βAPP by tacrine did not depend on its anticholinesterase activity and that tacrine operates via a noncholinergic mechanism.

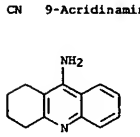
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of tacrine and physostigmine on secretion of β-amyloid precursor protein in cell lines)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



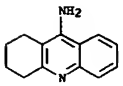
L11 ANSWER 68 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:427449 HCAPLUS
DOCUMENT NUMBER: 125:104949
TITLE: Facilitatory effect of huperzine-A on mouse neuromuscular transmission in vitro
AUTHOR(S): Lin, Jia-Hui; Hu, Guo-Yuan; Tang, Xi-Can
CORPORATE SOURCE: Shanghai Inst. Materia Medica, Chinese Academy Sciences, Shanghai, 200032, Peop. Rep. China
SOURCE: Zhongguo Yaoli Xuebao (1996), 17(4), 299-301
CODEN: CYLPDN; ISSN: 0253-9756
PUBLISHER: Kexue
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim was to study the effects of huperzine-A on neuromuscular junction transmission in mouse. The isolated mouse phrenic nerve-hemidiaphragm prepns. were used with the conventional intracellular recording technique. The spontaneous elec. activities of cholinergic nerve terminals (miniature end-plate potentials, MEPP) were recorded. Huperzine-A, tacrine, and E2020 at the concns. of 0.05-1 μmol·L-1 increased the amplitude, mean rise time, and half decay time of MEPP in a concn-dependent manner. Their potencies were E2020 > huprazine-A > tacrine. Thus, the anticholinesterase action of huprazine-A in cholinergic synapses is stronger than that of tacrine.

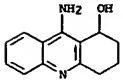
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of huperzine-A, tacrine and E2020 on neuromuscular transmission)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



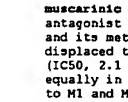
L11 ANSWER 69 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:395026 HCAPLUS
DOCUMENT NUMBER: 125:158303
TITLE: Biphasic effect of tacrine on acetylcholine release in rat brain via M1 and M2 receptors
AUTHOR(S): Svensson, Anne-Lie; Zhang, Xiao; Nordberg, Agneta
CORPORATE SOURCE: Department of Clinical Neuroscience and Family Medicine, Division of Nicotine Research, Karolinska Institutet, Huddinge University Hospital, B84, Huddinge, S-141 86, Swed.
SOURCE: Brain Research (1996), 726(1,2), 207-212
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rat cortical synaptosomes preloaded with [3H]choline were superfused and stimulated with K+ in order to investigate the effect of the cholinesterase inhibitor tacrine on the in vitro release of acetylcholine (ACh). Tacrine both increased (10-6 and 5 + 10-6M) and decreased(10-5-10-4M) the release of ACh in a concentration-dependent manner. The facilitatory effect of tacrine was prevented by atropine and the M1 antagonist pirenzepine, whereas the inhibitory effect was blocked by atropine and the M2 antagonist AF-DX 116. These results indicate that tacrine increases and decreases K+-stimulated ACh release in the brain via M1 and M2 muscarinic receptors, resp. The tacrine-induced enhancement of ACh release occurs at clin. relevant tacrine concns. and might therefore be of importance for the treatment of Alzheimer's disease.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brain acetylcholine release response to tacrine mediated by M1 and M2 muscarinic receptors)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



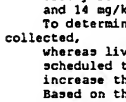
L11 ANSWER 70 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:383042 HCAPLUS
DOCUMENT NUMBER: 125:75250
TITLE: Identification of a 3-hydroxylated tacrine metabolite in rat and man: metabolic profiling implications and pharmacology
AUTHOR(S): Pool, William F.; Woolf, Thomas F.; Reily, Michael D.; Caprathe, Bradley W.; Emmerling, Mark R.; Jaen, Juan C.
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research Div., Warner-Lambert Company, Ann Arbor, MI, 48105, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(15), 3014-3018
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Discrepancies in urinary metabolic profiles in rats administered tacrine suggested the presence of an unidentified metabolite of tacrine. Chromatog. methods were developed that allowed isolation of a metabolite fraction containing both 1-hydroxytacrine and an unknown metabolite from rat urine. Mass spectral anal. indicated this metabolite to be a monohydroxylated derivative, which upon two dimensional COSY NMR anal. could be assigned as 3-hydroxytacrine. This structural assignment was confirmed by independent synthesis. 3-Hydroxytacrine was also identified as a human urinary metabolite of tacrine. Biol., this compound was found to have in vitro human red blood cell acetylcholinesterase inhibitory activity similar to that of 1- and 4-hydroxytacrine and approx. 8-fold less than that of tacrine. These results underscore the need to conduct rigorous structural identification studies, especially in cases where isomeric metabolites are possible, in assessing the accuracy of chromatog. profiling techniques.
IT 124027-47-0, 1-Hydroxytacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(identification of 3-hydroxylated tacrine metabolite in rat and human)
RN 124027-47-0 HCAPLUS
CN 1-Acridinol, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



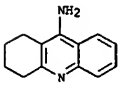
L11 ANSWER 71 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:293249 HCAPLUS
DOCUMENT NUMBER: 125:1129
TITLE: Effect of tacrine on in vivo release of dopamine and its metabolites in the striatum of freely moving rats
AUTHOR(S): Warpman, Ulrika; Zhang, Xiao; Nordberg, Agneta
CORPORATE SOURCE: Dep. Pharmaceutical Biosci., Uppsala Univ., Uppsala, S-751, Swed.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 277(2), 917-922
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tacrine (THA) on extracellular concns. of dopamine (DA), 3,4-dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindoleacetic acid were investigated in the striatum of freely moving rats, using a microdialysis technique in which tacrine was administered locally via the microdialysis membrane. THA in concns. of 10-8 to 10-5 M, significantly elevated the levels of the DA metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid, whereas a significantly increased content of extracellular DA was observed at higher concns. of THA (10-3 to 10-2 M). Local administration of the muscarinic antagonist atropine (10-6 M) or the nicotinic antagonist mecamylamine (10-5 M) both prevented the effects of THA on DA and its metabolites. In vitro receptor binding studies showed that THA displaced the binding of muscarinic antagonists [3H]pirenzepine (IC50, 2.1 ± 0.4 μM) and [3H]AFDX 384 (IC50, 3.4 ± 0.2 μM) equally in striatal tissue, suggesting that THA binds with equal affinity to M1 and M2 muscarinic receptor subtypes. THA showed a 20-fold lower affinity to high-affinity nicotinic receptors compared with muscarinic receptors when determined by [3H]cystine competition curves. The study indicated that THA enhances monoamine neurotransmission in the rat striatum, probably via an interaction with both muscarinic and nicotinic heteroreceptors.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tacrine effect on striatal dopamine and metabolites release in relation to monoamine neurotransmission enhancement via muscarinic and nicotinic heteroreceptor interaction)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



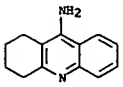
L11 ANSWER 72 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:263041 HCAPLUS
DOCUMENT NUMBER: 124:332862
TITLE: The aluminum hypothesis of Alzheimer disease: lack of effectiveness of tacrine and velnacrine as aluminum detoxifiers
AUTHOR(S): Domingo, Jose L.; Gomez, Mercedes; de la Torre, Antonio; Llobet, Juan M.; Corbella, Jacinto
CORPORATE SOURCE: School Medicine, "Rovira i Virgili" Univ., Reus, 43201, Spain
SOURCE: Research Communications in Pharmacology and Toxicology (1996), 1(1), 39-50
CODEN: RCPTFY; ISSN: 1087-1101
PUBLISHER: PJD Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of the present study was to assess whether tacrine and velnacrine, two drugs under investigation for Alzheimer disease (AD) therapy, might result in an addnl. benefit by diminishing the aluminum (Al) body burden. Two groups of male rats were loaded with Al by parenteral administration of Al nitrate at doses of 90 and 180 mg/kg/day for four or five weeks. At the end of the loading period, velnacrine and tacrine were administered orally for five and four consecutive days, resp., at doses of 0, 3.5, 7 and 14 mg/kg/day (velnacrine), or 0, 2.5, 5 and 10 mg/kg/day (tacrine). To determine Al excretion and tissue distribution, urine was daily collected, whereas liver, spleen, kidney, bone and brain samples were obtained at scheduled termination. Neither tacrine nor velnacrine were able to increase the urinary Al excretion or to reduce tissue Al concns. Based on the present results no other roles than the well established enhancement of cholinergic transmission in AD would be attributed to tacrine or velnacrine. However, according to recent reports the Al hypothesis of AD should not be discarded.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aluminum hypothesis of Alzheimer disease: lack of effectiveness of tacrine and velnacrine as aluminum detoxifiers)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 73 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:232437 HCAPLUS
DOCUMENT NUMBER: 124:307279
TITLE: Effects of cholinesterase inhibitors on neurotransmitter metabolism in the brain
AUTHOR(S): Ishii, Yutaka; Shibanoki, Shinji; Kubo, Taizo; Hata, Hideyo; Ishikawa, Koichi
CORPORATE SOURCE: School of Medicine, Nihon University, Tokyo, 173, Japan
SOURCE: Neurosciences (Okayama, Japan) (1995), 21(4), 167-80
CODEN: NUOCDO; ISSN: 0388-7448
PUBLISHER: Japan Neurosciences Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the effects of 9-amino-2,3,5,6,7,8-hexahydro-1 H-cyclopenta[b]quinoline monohydrochloride monohydrate (NIK-247), a novel cholinesterase (ChE) inhibitor, on the metabolism of acetylcholine (ACh) and monoamines in the dissected brains of rats using high performance liquid chromatog. and electrochem. detection. NIK-247 (10 or 30 mg/kg) produced significant, dose-dependent increases in the concns. of ACh, dihydroxyphenylacetic acid (DOPAC), 3-methoxy-4-hydroxyphenylethylene glycol (MOPEG) and 5-hydroxyindoleacetic acid (5-HIAA) in the dissected regions of the brain 2 h after administration. The effect of NIK-247 was still observable 4 h after its administration. Physostigmine (10 mg/kg) and tetrahydroaminoacridine (10 and 30 mg/kg) each increased the concns. of ACh and of monoamine turnover in the brain 2 h after the administration. These agents also increased the concns. of MOPEG, DOPAC, homovanillic acid (HVA) and 5-HIAA. Although aniracetam (300 mg/kg) also increased the concns. of 5-HIAA, calcium hopantenate had no significant influence on the concns. of ACh and amine-related substances. NIK-247 inhibited the activity of ChE (IC50 8 + 10-7 M), and, at high doses, (1 + 10-3,4 M) inhibited the activity of monoamine oxidases. It had no effect on the activity of choline acetyltransferase or tyrosine hydroxylase. Results suggest that NIK-247 increases the intracerebral concentration of ACh by inhibiting ChE, and that it accelerates the rate of monoamine turnover by activating cholinergic neurons.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of cholinesterase inhibitors on brain neurotransmitter metabolism)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

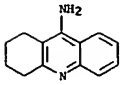


L11 ANSWER 74 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:89531 HCAPLUS
DOCUMENT NUMBER: 124:194072
TITLE: Cholinergic improvement of a naturally-occurring memory deficit in the young rat
AUTHOR(S): Smith, Richard D.; Kistler, Michael K.; Cohen-Williams, Mary; Coffin, Vicki L.
CORPORATE SOURCE: Kenilworth, NJ, 07033-0539, USA
SOURCE: Brain Research (1996), 707(1), 13-21
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In a single-trial, passive-avoidance response (PAR) paradigm, young rats at post-natal day (PND) 16 were found to exhibit a performance deficit that diminished progressively with age. When administered prior to training, single peripheral injections of cholinomimetic drugs, either a muscarinic agonist (arecoline, pilocarpine or oxotremorine), an acetylcholinesterase inhibitor (tacrine or E2020), or nicotine, increased the response latencies for young rats to that of adult levels in a dose-dependent manner (overall dose range = 0.003 μg/kg-10 mg/kg). Neither the cholinergic antagonists scopolamine, atropine or mecamylamine, nor a series of non-cholinergic drugs, diazepam, haloperidol, phenobarbital, pargyline, D-amphetamine, imipramine, piracetam or N-methyl-D-aspartate (NMDA) increased PAR latencies. When 0.1 mg/kg scopolamine was given to young rats prior to arecoline, the dose-effect curve for enhanced latency times was shifted to the right. Higher doses of scopolamine completely blocked the effects of arecoline. Scopolamine (0.001-1.0 mg/kg) administered subsequent to, rather than before PAR training, blocked the usual arecoline-induced enhancement of response latencies. Alternatively, consolidation could be facilitated with different doses of tacrine (0.0003-10 mg/kg). These results demonstrate that young rats fail to remember the PAR but that retention for this task can be specifically enhanced with cholinomimetic drugs.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cholinergic improvement of naturally-occurring memory deficit in young rat)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 75 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:76817 HCAPLUS
DOCUMENT NUMBER: 124:142671
TITLE: Amnesia induced in mice by centrally administered β-amyloid peptides involves cholinergic dysfunction
AUTHOR(S): Maurice, Tangui; Lockhart, Brian P.; Privat, Alain
CORPORATE SOURCE: Montpellier, 34063/1, Fr.
SOURCE: Brain Research (1996), 706(2), 181-93
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Substantial evidences suggest that the increased cerebral deposition, and neurotoxic action of the β-amyloid peptide, the major constituent of senile plaques, may represent the underlying cause of the cognitive deficits observed in Alzheimer's disease. Herein, the authors attempted to verify this hypothesis by inducing a potential Alzheimer's-type amnesia after direct intracerebroventricular administration of aggregated β25-35-amyloid peptide in mice. In this aim, amnesic capacities were evaluated after 6 to 13 days, using spontaneous alternation in the Y-maze, step-down type passive avoidance and place learning in a water-maze. Pre-training administration of aggregated β25-35 peptide induced dose-dependent decreases in both alternation behavior and passive avoidance, at doses of 3 and 9 nmol/mouse. A reduced but still significant impairment was observed when the peptide was not aggregated, or 'aged', by preincubation for 4 days at 37°. The β1-28 peptide, at 3 nmol/mouse, also induced a marked decrease in step-down latency. Post-training, but not pre-retention, administration of β25-35 peptide also significantly impaired learning. The beneficial effects of cholinergic agents on β25-35-induced amnesia was examined using the cholinesterase inhibitor tacrine (THA, 1.3 and 4.3 μmol/kg i.p.) and the nicotinic receptor agonist (-)-nicotine (NIC, 0.06 and 0.2 μmol/kg i.p.). Both drugs induced a dose-dependent abrogation of the β25-35-induced decreases in alternation behavior and passive avoidance. Furthermore, THA, at 1.3 μmol/kg, and NIC, at 0.2 μmol/kg, also reversed the β25-35-induced impairment of place learning and retention in the water-maze. Histol. examination of Cresyl violet-stained brain sections indicated a moderate but significant cell loss within the frontoparietal cortex and the hippocampal formation of mice treated with aged β25-35 peptide (9 nmol). Examination of Congo red-stained sections in the same animals demonstrated the presence of numerous amyloid deposits throughout these brain areas. These results confirm that the deposition of β-amyloid peptide in the brain is in some way related to impairment of learning and cholinergic degeneration and suggest that the [25-35] fragment of the β-amyloid protein, sufficient to induce neuronal death in cultures, also induces an Alzheimer's-type amnesia in mice.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-amyloid peptide-induced amnesia in mice prevention by treatment with tacrine and nicotine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 75 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 76 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

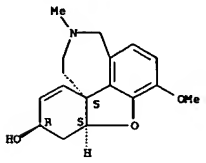
ACCESSION NUMBER: 1996:76124 HCAPLUS
DOCUMENT NUMBER: 124:107461
TITLE: Agonist responses of neuronal nicotinic acetylcholine receptors are potentiated by a novel class of allosterically acting ligands
AUTHOR(S): Schrattenholz, Andrej Pereira, Edna F. R.; Roth, Ulrich; Weber, Karl-Heinz; Albuquerque, Edson X.; Maelicke, Alfred
CORPORATE SOURCE: Med. Sch., Johannes-Gutenberg Univ., Mainz, D-55099, Germany
SOURCE: Molecular Pharmacology (1996), 49(1), 1-6
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Similar to the GABAA receptor and the N-methyl-D-aspartate subtype of glutamate receptor, neuronal nicotinic acetylcholine receptors are subject to pos. modulatory control by allosterically acting ligands. Exogenous ligands such as galanthamine and the neurotransmitter 5-hydroxytryptamine, when applied in submicromolar concns. with nicotinic agonists, significantly increase the frequency of opening of nicotinic receptor channels and potentiate agonist-activated currents. Because these effects have been shown to be blocked by the monoclonal antibody FK1, they are mediated by binding sites that are located on α subunits of nicotinic receptors and distinct from those for acetylcholine and acetylcholine-competitive ligands. At higher concns., the potentiating effect of these ligands decreases and is eventually overcome by an inhibition of the agonist-induced response. The sensitizing actions of galanthamine, 5-hydroxytryptamine, and related compds., at submicromolar concns., may reflect the existence of cross-talk between adjacent neuroreceptors and synapses in the central nervous system and thus suggests the formation of transiently active chemical networks in the vertebrate brain.

IT 357-70-0, Galanthamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(agonist responses of neuronal nicotinic acetylcholine receptors potentiation by allosterically acting ligands)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 76 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 77 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

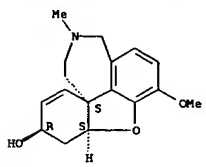
ACCESSION NUMBER: 1996:72041 HCAPLUS
DOCUMENT NUMBER: 124:136283
TITLE: Pharmacological testing of intracortical interneuronal connections
AUTHOR(S): Gassanov, U. G.; Martinson, Yu. L.; Khokhlova, V. N.
CORPORATE SOURCE: Inst. Higher Nervous Activity Neurophysiol., Moscow, Russia
SOURCE: Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova (1994), 44(6), 1016-25
CODEN: ZVNDAM; ISSN: 0044-4677
PUBLISHER: Nauka
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB An attempt is made to study the influence of acetylcholine on functional connections of cortical neurons and their frequency characteristics. Multiunit activity was recorded in the sensorimotor cortex of immobilized and freely moving rats. Cross correlation anal. was used. Influence of acetylcholine (Ach) and Ca-chelator ethyleneglycoltetraacetate (EGTA) on the functional characteristics of the neighboring neurons was studied in the first series of expts. The substances were iontophoretically applied to the sensorimotor cortex neurons of the immobilized unanesthetized rats. Application of Ach led to variation in the frequency characteristics of single neurons and in the majority cases did not affect the neuronal interrelations. EGTA application, independently on the background frequency of the neuronal activity, resulted in disappearance of interneuronal connections which recovered after the end of EGTA effect. The second series of expts. was carried out in freely moving rats. Systemic injection of galantamine essentially increased the frequency of activity of the cortical neurons not affecting their network activity. The authors suggest that intracortical relations can be realized independently on the extracortical influences which are manifested in variations in the background pulsation of the single neurons. Qual. estimation of Ach influence on the functional characteristics of the cortical neurons do not reveal Ach effects on formation of intracortical connections. These technique may be applied in further studies of intracortical neurons connections.

IT 357-70-0, Galantamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect on interneuronal connections in sensory cortex)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

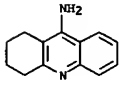


L11 ANSWER 77 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

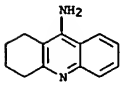
L11 ANSWER 78 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:71520 HCAPLUS
DOCUMENT NUMBER: 124:106701
TITLE: Composition and method for treating nicotine craving in smoking cessation
INVENTOR(S): Callaway, Enoch
PATENT ASSIGNEE(S): University of California, USA
SOURCE: U.S., 6 pp. Cont.-in-part of U.S. Ser. No. 121,606, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5480651	A	19960102	US 1994-213111	19940315
WO 9507690	A1	19950323	WO 1994-US10328	19940913
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRIORITY APPLN. INFO.:			US 1992-851914	B2 19920316
			US 1993-121606	B2 19930915
			US 1994-213111	A 19940315

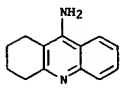
AB A method for relieving craving in a nicotine-habituated patient and a composition for treating the patient, are provided. The composition administered has a non-specific acetylcholine agonist and a muscarinic agonist. A particularly preferred composition for relieving craving takes the form of a tablet where the first component is a water-soluble physostigmine and the second component is a water-soluble scopolamine. Tablets containing scopolamine HBr, physostigmine sulfate, and ascorbic acid were formulated. Patients treated reported a slight increase in alertness and a diminished craving for nicotine.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetylcholine agonist and muscarinic agonist for treatment of nicotine addiction)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 79 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:41921 HCAPLUS
DOCUMENT NUMBER: 124:135514
TITLE: Tetrahydro-9-aminoacridine has mixed actions on muscarinic currents and blocks opioid currents in rat locus ceruleus neurons
AUTHOR(S): Osborne, Peregrine B.; Christie, MacDonald J.
CORPORATE SOURCE: Department of Pharmacology D06, The University of Sydney, Sydney, Australia
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 276(1), 137-42
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Actions of tetrahydro-9-aminoacridine (THA) on membrane properties of locus ceruleus neurons were examined using intracellular recording in superfused brain slices. Low concns. of THA (300 nM-3 μM) caused a small inward current and a 10-fold increase in the potency of ACh to produce inward (excitatory) currents. No effect was seen on currents activated by carbachol, a muscarinic agonist not degraded by cholinesterases. High concns. of THA (30-300 μM) caused larger inward currents and a decrease in cell conductance. At these concns. THA inhibited inward currents induced by carbachol (IC50 = 33 μM) and by substance P, which reportedly excites locus ceruleus neurons via the same ionic mechanism as muscarinic agonists. Furthermore, outward currents activated by opioids could be completely blocked (IC50 = 15 μM). Also affected was the action potential waveform, which was slower to rise, longer in duration and smaller in amplitude. The results suggested that THA has predominantly excitatory effects on locus ceruleus neurons - both by greatly enhancing the actions of Ach and by producing a small inward current. At high concns. effects are mixed and include inhibition of muscarinic currents, as well as of resting and agonist-induced inwardly rectifying potassium currents. The block of opioid currents by THA was not consistent with inhibition of a cationic conductance as recently proposed.
IT 321-64-2, THA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tetrahydro-9-aminoacridine has mixed actions on muscarinic currents and blocks opioid currents in rat locus ceruleus neurons)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

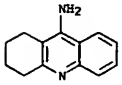


L11 ANSWER 80 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:13939 HCAPLUS
DOCUMENT NUMBER: 124:83880
TITLE: Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease
AUTHOR(S): Poirier, Judes; Delisle, Marie-Claude; Quirion, Remi; Aubert, Isabelle; Farlow, Martin; Lahiri, Debmoi; Hui, Siu; Bertrand, Philippe; Nalbantoglu, Josephine; et al.
CORPORATE SOURCE: McGill Cent. Stud. Aging, McGill Univ., Montreal, QC, H4H 1R3, Can.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(26), 12260-4
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Apolipoprotein E (apoE) is critical in the modulation of cholesterol and phospholipid transport between cells of different types. Human apoE is a polymorphic protein with three common alleles, APOe2, APOe3, and APOe4. ApoE4 is associated with sporadic and late-onset familial Alzheimer disease (AD). Gene dose was shown to have an effect on risk of developing AD, age of onset, accumulation of senile plaques in the brain, and reduction of choline acetyltransferase (ChAT) activity in the hippocampus of AD subjects. To characterize the possible impact of the apoE4 allele on cholinergic markers in AD, the authors examined the effect of apoE4 allele copy number on pre- and postsynaptic markers of cholinergic activity. ApoE4 allele copy number showed an inverse relation with residual brain ChAT activity and nicotinic receptor binding sites in both the hippocampal formation and the temporal cortex of AD subjects. AD cases lacking the apoE4 allele showed ChAT activities close or within age-matched normal control values. The effect of the apoE4 allele on cholinomimetic drug responsiveness was assessed next in a group of AD patients who completed a double-blind, 30-wk clin. trial of the cholinesterase inhibitor tacrine. Results showed that >80% of apoE4-neg. AD patients showed marked improvement after 30 wks as measured by the AD assessment scale (ADAS), whereas 60% of apoE4 carriers had ADAS scores that were worse compared to baseline. These results strongly support the concept that apoE4 plays a crucial role in the cholinergic dysfunction associated with AD and may be a prognostic indicator of poor response to therapy with acetylcholinesterase inhibitors in AD patients.
IT 321-64-2, Tacrine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(apolipoprotein E4 allele as predictor of cholinergic deficits and outcome of treatment with tacrine in Alzheimer disease in humans)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



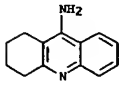
L11 ANSWER 81 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:8997 HCAPLUS
DOCUMENT NUMBER: 124:106364
TITLE: Metabolic response to tacrine (THA) and physostigmine in the aged rat brain
AUTHOR(S): Bassant, M. H.; Jazat-Poindessous, F.; Lamour, Y.
CORPORATE SOURCE: INSERM U161, Paris, 75014, Fr.
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1995), 15(6), 1093-102
CODEN: JCBMDN; ISSN: 0271-678X
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of the centrally acting anticholinesterases tacrine (tetrahydroaminoacridine, THA) and physostigmine (PHY), on local cerebral glucose utilization (LCGU) have been studied in 27-mo-old rats, using the autoradiog. [14C]deoxyglucose technique. THA (10 mg/kg i.p.) increased LCGU significantly in 13 of the 54 regions studied (24%) including insular, parietal, temporal, and retrosplenial cortices, septohippocampal system, thalamus, lateral habenula, and superior colliculus. In these regions, the average THA-induced increase in LCGU was 24% above control. The whole brain mean LCGU was not significantly increased. PHY (0.5 mg/kg) increased LCGU in 18% of the regions (average elevation 23%). The whole brain mean LCGU increased by 7% ($p < 0.05$). The regional distributions of THA- and PHY-induced increases in LCGU were extremely similar and overlapped the distribution of the M2 muscarinic receptors and that of acetylcholinesterase activity, suggesting that the major effects of THA and PHY on LCGU result from their anticholinesterase action. As compared to those of 3-mo-old rats, both the number of regions affected and the amplitude of the metabolic activation were significantly less in aged rats. However, the drugs were still active in old rats and compensated for the age-related hypometabolism in some brain areas.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic response to tacrine and physostigmine in the aged rat brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 82 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:6908 HCAPLUS
DOCUMENT NUMBER: 124:105610
TITLE: A Comparative Molecular Field Analysis Study of N-Benzylpiperidines as Acetylcholinesterase Inhibitors
AUTHOR(S): Tong, Weida; Collantes, Elizabeth R.; Chen, Yu; Welsh, William J.
CORPORATE SOURCE: Department of Chemistry, University of Missouri, St. Louis, MO, 63121, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(2), 380-7
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 1-benzyl-4-[2-(N-benzoylamino)ethyl]piperidine derivs. and of N-benzylpiperidine benzisoxazoles have been investigated using the comparative mol. field anal. (CoMFA) approach. These compds. have been found to inhibit the metabolic breakdown of the neurotransmitter acetylcholine (ACh) by the enzyme acetylcholinesterase (AChE) and hence alleviate memory deficits in patients with Alzheimer's disease by potentiating cholinergic transmission. Development of the CoMFA model considered two sep. alignments: (i) alignment I which emphasized the electrostatic fitting of the subject compds. and (ii) alignment II which emphasized their steric fitting. In addition, the inhibitor compds. were considered both as neutral species and as N-piperidine-protonated species. The resulting 3D-QSAR indicates a strong correlation between the inhibitory activity of these N-benzylpiperidines and the steric and electronic factors which modulate their biochem. activity. A CoMFA model with considerable predictive ability was obtained.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative mol. field anal. study of N-benzylpiperidines as acetylcholinesterase inhibitors)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

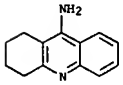


L11 ANSWER 83 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:959294 HCAPLUS
DOCUMENT NUMBER: 124:45541
TITLE: Effects of (-)-S-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane L-tartrate monohydrate (YM796), a novel muscarinic agonist, on disturbance of passive avoidance learning behavior in drug-treated and senescence-accelerated mice
AUTHOR(S): Suzuki, Masanori; Yamaguchi, Takashi; Ozawa, Yukiko; Ohyama, Mitsuko; Yamamoto, Minoru
CORPORATE SOURCE: Clinical Pharmacology Research Laboratory, Yamanouchi Pharmaceutical Co. Ltd., Tokyo, 174, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 275(2), 728-36
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Effects of YM796 (-)-S-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane L-tartrate monohydrate; a novel muscarinic agonist, were observed on disturbance of passive avoidance learning behavior in drug (protein synthesis inhibitor and anticholinergic drugs)-treated and senescence-accelerated mice in comparison with those of a muscarinic agonist (AF102B) and acetylcholinesterase inhibitors (E2020 [1-benzyl-4-[(5,6-dimethoxy-1-indanone-2-yl) methyl] piperidine hydrochloride), NIK247 [9-amino-2,3,4,5,6,8-hexahydro-1H-cyclopenta(b)-quinoline monohydrate hydrochloride], THA (9-amino-1,2,3,4-tetrahydroacridine) and physostigmine). All tested drugs administered before training significantly prolonged the shortened latency of step-through induced by the protein synthesis inhibitor cycloheximide (150 mg/kg s.c.). This shortened latency was also significantly prolonged when YM796 was administered immediately after training, but not when administered before the test trial. The ameliorating effect of YM796 on the impairment in learning behavior by cycloheximide was significantly suppressed by pirenzepine (0.1 μg/mouse i.c.v.). When administered before training, all test drugs prolonged the shortened latency of step-through induced by treatment with the anticholinergic drugs [scopolamine (1 mg/kg s.c.) and hemicholinium-3 (0.3 μg/mouse i.c.v.)], suggesting that they ameliorated the impairment of learning behavior. This shortened latency in scopolamine-treated mice was also significantly prolonged by YM796, AF102B, E2020, NIK247 and physostigmine when administered immediately after training but not when administered before the test trial in hemicholinium-3-treated mice were similar to those in scopolamine-treated mice. The ameliorating effect of YM796 on the impaired learning behavior induced by scopolamine and hemicholinium-3 was significantly suppressed by administration of the M2 antagonist pirenzepine. YM796 ameliorated the impaired learning behavior induced by scopolamine (0.5, 1 and 2 mg/kg s.c.)-treated mice to a similar extent. The latency of step-through in SAMP8//YAN (SAM-P/8, senescence-accelerated-prone substrain) was shorter than that in SAMR1/YAN (SAM-R/1, senescence-accelerated-resistant substrain). YM796, AF102B and NIK247 significantly prolonged the shortened latency of step-through in SAMP8//YAN. In contrast, amitriptyline, with monoaminergic facilitatory and anticholinergic properties, had no effect on this impaired learning behavior. These results suggest that YM796 improves brain dysfunction in drug-treated and senescence-accelerated mice presumably by facilitation of the central cholinergic system.

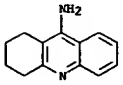
L11 ANSWER 83 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of muscarinic agonist YM796 and other cholinergic agonists on disturbance of passive avoidance learning behavior in drug-treated and senescence-accelerated mice)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



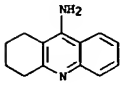
L11 ANSWER 84 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:952625 HCAPLUS
DOCUMENT NUMBER: 124:83832
TITLE: The effect of acetylcholinesterase inhibitors on acetylcholinesterase in senile plaque, normal human or rat brain, human erythrocyte or rat skeletal muscle
AUTHOR(S): Nakamura, S.; Yukawa, M.; Mimori, Y.
CORPORATE SOURCE: School Medicine, Hiroshima University, Hiroshima, 734, Japan
SOURCE: Advances in Behavioral Biology (1995), 44(Alzheimers and Parkinsons Diseases), 283-90
CODEN: ADBBBW; ISSN: 0099-6246
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, the five acetylcholinesterase inhibitors investigated were found to exert decreased effect on acetylcholinesterase in the senile plaque in comparison to normal brain or skeletal muscle. The results suggest that the property of acetylcholinesterase present in senile plaque is different from that in normal brain or skeletal muscle.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acetylcholinesterase inhibitors effect on acetylcholinesterase in senile plaque vs. normal human brain, erythrocyte, and muscle)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 85 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:952623 HCAPLUS
DOCUMENT NUMBER: 124:45523
TITLE: Does tacrine increase acetylcholine release from the hippocampus?
AUTHOR(S): Suzuki, Takeshi; Kawashima, Koichiro
CORPORATE SOURCE: Department Pharmacology, Kyoritsu College Pharmacy, Tokyo, 105, Japan
SOURCE: Advances in Behavioral Biology (1995), 44(Alzheimers and Parkinsons Diseases), 267-73
CODEN: ADBBBW; ISSN: 0099-6246
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It was found that a high dose of tacrine enhances the central cholinergic activity by both inhibition of cholinesterase activity and increase of acetylchiline release.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(tacrine enhancement of central cholinergic activity by inhibition of cholinesterase activity and increase of acetylchiline release)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

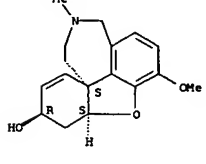


L11 ANSWER 86 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:750049 HCAPLUS
DOCUMENT NUMBER: 123:188316
TITLE: Cholinesterase inhibitors proposed for treating dementia in Alzheimer's disease: selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase
AUTHOR(S): Pacheco, G.; Palacios-Esquivel, R.; Moss, D. E.
CORPORATE SOURCE: Laboratory of Psychobiochemistry, University of Texas at El Paso, El Paso, TX, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 274(2), 767-70
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One consistent finding in senile dementia of the Alzheimer's type is that the brain has reduced ability to synthesize acetylcholine. This has been related, in part, to memory dysfunctions. Although a cholinergic deficient is not singularly responsible for symptoms of dementia, treatment strategies have been designed to facilitate cholinergic activity by inhibiting acetylcholinesterase (AChE). To minimize toxicity, however, a cholinesterase inhibitor selective for only AChE would be an ideal treatment. The purpose of this study was to determine the selectivity of physostigmine, metrifonate, methanesulfonyl fluoride and tetrahydroaminoacridine (tacrine) toward AChE as compared with butyrylcholinesterase (BChE) in human cortex. The results show that methanesulfonyl fluoride is selective as an inhibitor of AChE as compared with BChE. Physostigmine inhibited AChE more than BChE. Metrifonate was found to inhibit BChE more than AChE. Tetrahydroaminoacridine inhibited both enzymes in a complex way.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cholinesterase inhibitors for treating dementia in Alzheimer's disease: selectivity toward human brain acetylcholinesterase compared with butyrylcholinesterase)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 87 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:746791 HCAPLUS
DOCUMENT NUMBER: 123:285727
TITLE: Synthesis and Evaluation of 5-Amino-5,6,7,8-tetrahydroquinolinones as Potential Agents for the Treatment of Alzheimer's Disease
AUTHOR(S): Fink, David M.; Bores, Gina M.; Effland, Richard C.; Huger, Francis P.; Kurys, Barbara E.; Rush, Douglas K.; Selk, David E.
CORPORATE SOURCE: Department of Medicinal Chemistry, Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ, 08876, USA
SOURCE: Journal of Medicinal Chemistry (1995), 38(18), 3645-51
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 5-amino-5,6,7,8-tetrahydroquinolinones was designed and synthesized as acetylcholinesterase inhibitors. The compds. are related to huperzine A, a naturally occurring cholinesterase inhibitor. They inhibit acetylcholinesterase in vitro, and many are active in vivo in reversing a scopolamine-induced impairment of 24 h memory in a passive avoidance paradigm. Although these compds. were designed as partial structures of huperzine A, it is unlikely that they bind to the enzyme in a similar fashion, since they lack the unsatd. three-carbon bridge of huperzine A and both the quinolinone nitrogen and the amino group must be substituted in order to obtain good enzyme affinity.
IT 357-70-0D, Galanthamine, analogs or derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 5-aminotetrahydro-2-quinolinones as acetylcholinesterase inhibitors)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

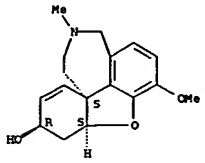
Absolute stereochemistry. Rotation (-).



L11 ANSWER 88 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:739237 HCAPLUS
DOCUMENT NUMBER: 123:160697
TITLE: Physostigmine, galanthamine and codeine act as 'noncompetitive nicotinic receptor agonists' on clonal rat pheochromocytoma cells
AUTHOR(S): Storch, Alexander; Schrattenholz, Andre; Cooper, Julia C.; Abdel Ghani, El Moeiz; Gutbrod, Oliver; Weber, Karl-Heinz; Reinhardt, Sigrid; Lobron, Christina; Hermsen, Bernhard; et al.
CORPORATE SOURCE: Laboratory of Molecular Neurobiology, Institute of Physiological Chemistry and Pathobiochemistry, Johannes Gutenberg University Medical School, Duesbergweg 6, Mainz, 55099, Germany
SOURCE: European Journal of Pharmacology, Molecular Pharmacology Section (1995), 290(3), 207-19
CODEN: EJPPET; ISSN: 0922-4106
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The acetylcholine esterase inhibitor (-)-physostigmine has been shown to act as agonist on nicotinic acetylcholine receptors from muscle and brain, by binding to sites on the α-polypeptide that are distinct from those for the natural transmitter acetylcholine (Schroeder et al., 1994). In the present report we show that (-)-physostigmine, galanthamine, and the morphine derivative codeine activate single-channel currents in outside-out patches excised from clonal rat pheochromocytoma (PC12) cells. Although several lines of evidence demonstrate that the three alkaloids act on the same channels as acetylcholine, the competitive nicotinic antagonist methyllycaconitine only inhibited channel activation by acetylcholine but not by (-)-physostigmine, galanthamine or codeine. In contrast, the monoclonal antibody FK1, which competitively inhibits (-)-physostigmine binding to nicotinic acetylcholine receptors, did not affect channel activation by acetylcholine but inhibited activation by (-)-physostigmine, galanthamine and codeine. The three alkaloids therefore act via binding sites distinct from those for acetylcholine, in a 'noncompetitive' fashion. The potency of (-)-physostigmine and related compds. to act as a noncompetitive agonist is unrelated to the level of acetylcholine esterase inhibition induced by these drugs. (-)-Physostigmine, galanthamine and codeine do not evoke sizable whole-cell currents, which is due to the combined effects of low open-channel probability, slow onset and slow inactivation of response. In contrast, they sensitize PC12 cell nicotinic receptors in their submaximal response to acetylcholine. While the abundance of nicotinic acetylcholine receptor isoforms expressed in PC12 cells excludes identification of specific nicotinic acetylcholine receptor subtypes that interact with noncompetitive agonists, the identical patterns of single-channel current amplitudes observed with acetylcholine and with noncompetitive agonists suggested that all PC12 cell nicotinic acetylcholine receptor subtypes that respond to acetylcholine also respond to noncompetitive agonist. The action of noncompetitive agonists therefore seems to be highly conserved between nicotinic acetylcholine receptor subtypes, in agreement with the high level of structural conservation in the sequence region harboring major elements of this site.
IT 357-70-0, Galanthamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(physostigmine, galanthamine and codeine act as noncompetitive

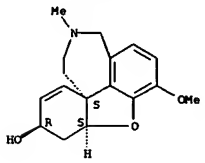
L11 ANSWER 88 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
nicotinic receptor agonists on clonal rat pheochromocytoma cells)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 89 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(pharmaceutical compns. for treatment of neurol. diseases contg.)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 89 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:723143 HCAPLUS
DOCUMENT NUMBER: 123:102794
TITLE: Pharmaceutical compositions and use thereof for treatment of neurological diseases and etiologically related symptomatology.
INVENTOR(S): Shapiro, Howard K.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 155 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9501096	A1	19950112	WO 1994-US7277	19940628
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5668117	A	19970916	US 1993-62201	19930629
AU 9472144	A1	19950124	AU 1994-72144	19940628
AU 692454	B2	19980611		
EP 707446	A1	19960424	EP 1994-921405	19940628
R: DE, FR, GB, IT				
JP 08512055	T2	19961217	JP 1994-503597	19940628
PRIORITY APPLN. INFO.:			US 1993-62201 A	19930629
			US 1991-660561 B1	19910222
			US 1993-26617 B2	19930223
			WO 1994-US7277 W	19940628

AB Pharmaceutical compns. for treatment of several neurol. diseases and pathophysiol.-related symptomol. in other body tissues, including peripheral neuropathies, secondary symptomol. of diabetes, Alzheimer's disease, Parkinson's disease, alc. polyneuropathy and age-onset symptomol., as well as analogous veterinary diseases, are disclosed. Spurious pathol. chemical crosslinking of normal intracellular structures is a fundamental aspect of these neurol. diseases. Covalent bond crosslinking of protein and lipid subcellular elements appear to underlie the formation of polymerized aggregates of neurofilaments and other structural proteins, and lipofuscin. Pharmacol. intervention in some neurol. diseases using water-soluble, small mol. weight primary amines or their derivs. as oral therapeutic agents, may compete with cellular protein and lipid amine groups for reaction with disease-induced carbonyl-containing aliphatic and aromatic hydrocarbons. Primary pharmacol. agents include 4-aminobenzoic acid and derivs. thereof to facilitate kidney recognition and removal. This invention also includes oral use of nonabsorbable polyamine polymers and amine-related co-agents, such as chitosan, to covalently bind and sequester potentially toxic carbonyl compds. present in the diet, oral use of known antioxidant co-agents and related nutritional factors and use of the primary agent and co-agents in combination with known medicaments for treatment of these neurol. diseases.
IT 357-70-0, Galanthamine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

L11 ANSWER 90 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:695942 HCAPLUS
DOCUMENT NUMBER: 123:83218
TITLE: Memory enhancing 9-aminotetrahydroacridines and related compounds
INVENTOR(S): Shutske, Gregory M.; Helsley, Grover C.; Kapples, Kevin J.
PATENT ASSIGNEE(S): Hoechst-Roussel Pharmaceuticals Inc., USA
SOURCE: U.S., 10 pp. Cont.-in-part of U.S. Ser. No. 26,730, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5391553	A	19950221	US 1988-244212	19880914
FI 8801223	A	19880918	FI 1988-1223	19880315
FI 91401	B	19940315		
FI 91401	C	19940627		
IL 85741	A1	19960514	IL 1988-85741	19880315
AU 8813141	A1	19880915	AU 1988-13141	19880316
AU 608300	B2	19910328		
DK 8801435	A	19880918	DK 1988-1435	19880316
DK 172864	B1	19990823		
NO 8801164	A	19880919	NO 1988-1164	19880316
NO 173498	B	19930913		
NO 173498	C	19931222		
JP 63238063	A2	19881004	JP 1988-60665	19880316
JP 2888485	B2	19990510		
HU 46672	A2	19881128	HU 1988-1254	19880316
HU 201018	B	19900928		
ZA 8801865	A	19881130	ZA 1988-1865	19880316
CA 1318675	A1	19930601	CA 1988-561561	19880316
AU 9068239	A1	19910314	AU 1990-68239	19901219
AU 634004	B2	19930211		
AU 9068241	A1	19910314	AU 1990-68241	19901219
AU 635370	B2	19930318		
AU 9068240	A1	19910502	AU 1990-68240	19901219
AU 633668	B2	19930204		
PRIORITY APPLN. INFO.:			US 1987-26730 B2	19870317
OTHER SOURCE(S):	MARPAT 123:83218			

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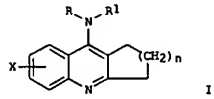


I

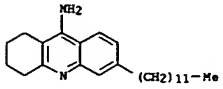
AB There are disclosed compds. having the formula I wherein n is 1-4; X is alkyl of 3-18 carbon atoms, cycloalkyl of 3-7 carbon atoms or cycloalkylloweralkyl; R is hydrogen, loweralkyl or loweralkylcarbonyl; R1 is hydrogen, loweralkyl, loweralkylcarbonyl, aryl,

L11 ANSWER 90 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
diloweralkylaminoloweralkyl, arylloweralkyl, diarylloweralkyl, oxygen-bridged arylloweralkyl or oxygen-bridged diarylloweralkyl; stereo isomers thereof and pharmaceutically acceptable acid addn. salts thereof, which are useful for enhancing memory, methods for synthesizing them, and pharmaceutical compns. comprising an effective memory enhancing amt. of such a compd. Thus, e.g., reaction of 9-chloro-7-cyclohexyl-1,2,3,4-tetrahydroacridine (prepn. given) with NH3 followed by salt formation afforded 9-amino-7-cyclohexyl-1,2,3,4-tetrahydroacridine hydrochloride which at 0.63 mg/kg s.c. reversed scopolamine-induced memory deficit in 20% of mice tested.

IT 165249-09-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(memory enhancing 9-aminotetrahydroacridines and related compds.)

RN 165249-09-2 HCAPLUS

CN 9-Acridinamine, 6-dodecyl-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 91 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:640415 HCAPLUS

DOCUMENT NUMBER: 123:47743

TITLE: Action on noradrenergic transmission of an anticholinesterase: 9-amino-1,2,3,4-tetrahydroacridine

AUTHOR(S): Vivas, N. M.; Marmol, F.; Salles, J.; Badia, A.; Diersseen, M.

CORPORATE SOURCE: Departament Farmacologia Psiquiatria, Universitat Autonoma Barcelona, Bellaterra, 08193, Spain

SOURCE: Neuropharmacology (1995), 34(4), 367-75
CODEN: NEPHBW; ISSN: 0028-3908

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

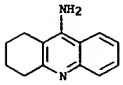
LANGUAGE: English

AB The mechanism by which 9-amino-1,2,3,4-tetrahydroacridine (THA) inhibits β-adrenoceptor linked cAMP formation and its possible relationship with the cholinergic system were studied. In addition, the effect of THA on α1-adrenoceptor coupled transduction systems was also investigated. THA was not able to influence the concentration-response curve for forskolin indicating that it is not acting on the catalytic subunit of the adenylate cyclase complex. On the other hand a cholinergic component seems to participate in the action of THA on β-adrenoceptor stimulated adenylate cyclase activity since the blockade of muscarinic receptors with atropine (10 μM) partially prevented the reduction in cAMP formation attained by THA in the hippocampus, in isoprenaline-stimulated conditions. This effect is not reproducible by another potent anticholinesterase physostigmine. Moreover, THA at concns. up to micromolar did not affect A1-adrenoceptor stimulated cAMP formation or phosphoinositide hydrolysis. In conclusion, the neuropharmacol. profile of THA is not to be restricted to the cholinergic system and its effectiveness in improving age-associated cognitive deterioration may involve
an action on the β-adrenoceptor coupled signal transduction system. Moreover, the action of THA on the β-adrenergic and cholinergic systems in the brain could be relevant to the amelioration of cognitive deterioration and could lead to the development of new therapeutic strategies.

IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(action on noradrenergic transmission of anticholinesterase 9-amino-1,2,3,4-tetrahydroacridine)

RN 321-64-2 HCAPLUS

CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 92 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:608553 HCAPLUS

DOCUMENT NUMBER: 123:47836

TITLE: Effects of tetrahydroaminoacridine and nicotine in nucleus basalis and serotonin-lesioned rats

AUTHOR(S): Riekkinen, Paavo Jr.; Riekkinen, Minna

CORPORATE SOURCE: Department of Neurology, Canthia Building, University of Kuopio, P.O. Box 1627, Kuopio, FIN-70211, Finland

SOURCE: European Journal of Pharmacology (1995), 279(1), 65-73
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

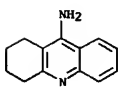
LANGUAGE: English

AB The present study was designed to investigate the hypothesis that concurrent degeneration of serotonin and acetylcholine cells may decrease the therapeutic effects of cholinergic drugs on cognitive functioning in Alzheimer dementia. Therefore, we compared the effects of pretraining injections of a cholinesterase inhibitor, tetrahydroaminoacridine (1, 3 and 5 mg/kg i.p.), and nicotine (0.03, 0.1 and 0.3 mg/kg i.p.) on spatial navigation (water maze) and passive avoidance in nucleus basalis- and nucleus basalis+p-chlorophenylalanine-lesioned rats. Nicotine (0.1 and 0.3 mg/kg) promoted passive avoidance performance of nucleus basalis-lesioned rats, but nicotine did not improve performance of combined-lesioned rats. Tetrahydroaminoacridine (3 mg/kg) facilitated passive avoidance performance of nucleus basalis- and combined-lesioned rats. However, tetrahydroaminoacridine-treated nucleus basalis + p-chlorophenylalanine-lesioned rats were not performing better than vehicle-treated nucleus basalis-lesioned rats. Spatial navigation of nucleus basalis and nucleus basalis+p-chlorophenylalanine-lesioned rats was slightly impair ed during the first training day and tetrahydroaminoacridine 3 mg/kg restored the performance of combined-lesioned rats. Combined-lesioned rats performed as well as the controls during the other training days. The present results suggest that, in Alzheimer's disease, combined degeneration of nucleus basalis cholinergic and brainstem serotonergic cells decreases the therapeutic effect of nicotine, but not that of tetrahydroaminoacridine.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of tetrahydroaminoacridine and nicotine in nucleus basalis and serotonin-lesioned rats)

RN 321-64-2 HCAPLUS

CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 93 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:601407 HCAPLUS

DOCUMENT NUMBER: 123:766

TITLE: Tetrahydro-9-aminoacridine presynaptically inhibits glutamatergic transmission in the rat amygdala

AUTHOR(S): Wang, Su-Jane; Huang, Chiung-Chun; Gean, Po-Wu

CORPORATE SOURCE: College Medicine, National Cheng-Kung University, Tainan, Taiwan

SOURCE: Brain Research Bulletin (1995), 37(3), 325-7
CODEN: BRBUDU; ISSN: 0361-9230

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

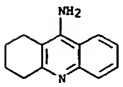
LANGUAGE: English

AB The effect of the centrally active anticholinesterase inhibitor tetrahydro-9-aminoacridine (THA) on synaptic transmission was studied in rat amygdala neurons in the in vitro slice preparation THA reversibly suppressed the excitatory postsynaptic potential (EPSP) in a concentration-dependent manner. Postsynaptic depolarization induced by α-amino-5-methyl-4-isoxazole propionate (AMPA) was not decreased by THA. These results demonstrate that THA has a presynaptic inhibitory action on the physiol. of synaptic transmission in the amygdala. Pretreating the slices with atropine did not affect THA's effect, indicating that the presynaptic muscarinic receptors are not involved.

IT 321-64-2, THA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetrahydroaminoacridine presynaptically inhibits glutamatergic transmission in rat amygdala)

RN 321-64-2 HCAPLUS

CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 94 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:575708 HCAPLUS
TITLE: Cholinergic therapies for Alzheimer's disease
AUTHOR(S): Davis, R. E.; Doyle, P. D.; Carroll, R. T.; Emmerling, M. R.; Jaen, J.
CORPORATE SOURCE: Applied Genetics, San Diego, CA, USA
SOURCE: Arzneimittel-Forschung (1995), 45(3a), 425-31
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Cantor
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Loss of cholinergic function in the neocortex and hippocampus arising from death or atrophy of basal forebrain cholinergic neurons is a consistent featur of the Alzheimer brain at autopsy or biopsy. Replacement of lost cholinergic function, therefore, may be of therapeutic benefit to the Alzheimer's (AD) patients. This can be accomplished by enhancign endogenous levels of **acetylcholine** (ACh) through inhibition of its degradation by acetylcholinesterase on by directly mimicking its actions at postslynaptic **muscarinic** receptors. Initial efforts focused on inhibition of cholinesterase activity with tacrine (1,2,3,4-tetrahydroaminoacridine monochloride, CAS 1684-40-8, THA, Cognex). Tacrine is a mixed, reversible inhibitor of cholinesterase activity that binds newar but not to the catalytically active serine in the active site of the enzyme. Through this action tacrine indirectly elevates ACh levels in the brains of animals and improves cognitive performance in rodents and monkeys. More importantly, tacrine has been shown to significantly improve several measures of cognitive performance in probable AD patients in well-controlled clin. trials, although not all patients respond to this agent. CI-979 ((E)-1,2,5,6-tetrahydro-1-methyl-3-pyridinecarboxaldehyde-O-Me oxime, CAS 139886-04-7) is a non-subtype selective, partial **muscarinic** agonist that enhances cognitive performance and increases central cholinergic activity in rodents at doses below those required to increase peripheral cholinergic tone. In normal healthy volunteers, CI-979 is well tolerated at single and multiple doses (q 6 h) up to 1.0 mg. Expected signs of mild to moderate peripheral cholinergic stimulation were noted at 0.5 to 1.0 mg doses (q 6 h). Dose limiting gastointestinal symptoms (i.e. stomach pain and emesis) were seen at the 2 mg/q 6 h dose. Aged normal volunteers and Alzheimer's patients tolerated higher doses when the dose was gradually escalated. GI symptoms became dose limiting at doses between 2.0 and 3 mg/q 6 h. The side-effect profile was qual. similar in yound and aged volunteers and AD patients. CI-979 is being investigated in a large multicenter trial as an antidementia agent. While the effect of tacrine and CI-979 on disease progression have not been carefully evaluated, activation of cell-surface **muscarinic** receptors by ACh or direct **muscarinic** agonists has been shown to control the processing of the amyloid precursor protein in a variety of cell lines. The **muscarinic** agonists carbachol and CI-979 have been shown to increase secretion of non-amyloid containing, N-terminal fragmetns of APP (APPs) into the culture media of cells transfected with m1 and m3 but not m2 and m4 receptors. **Muscarinic** control of APPs release can be mediated through phospholipase C (plC) but not adenylate cyclase linked receptors. APPs secretion is enhanced by phorbol esters, presumably through activation of protein kinases. Addnl., APPs release is enhanced by raising and is decreased by lowering intracellular Ca++ levels. Slowing protein transport from the endoplasmatic reticulum to the Golgi abolishes basal and carbachol-stimualted release of APPs from Chinese hamster ovary cells transfected with the human m1 **muscarinic** receptor. This suggest that **muscarinic** agonists stimulate the release of newly synthesized and transported APPs. Down-regulation of **muscarinic** receptors by rior exposure to carbachol blocked the ability of **muscarinic** agonists and phorbol esters to increase APPs secretion. In contrast, down-regulation of protein kinases with PMA blocked phorbol-ester but not carbachol-stimulated release of APPs, indicating that activation of pkC activity is not required for carbachol-stimualted secretion of APPs. Further, activation of phospholipase A2 (plA2) by mellitin also increases APPs release and antagonists of PLA2 block mellitin and carbachol-stimulated release of APPs. Thus, **muscarinic** agonists after the processing of APP through both phorbol ester sensitive an dinsensitive signalling pathways. Loss of synaptic efficacy at plC- and plA2-linked receptor, therefore, may contribute to altered processing of APP and ultimately the pathogenesis of AD. The possibility exists that cholinomimeticdcs like tacrine and CI-979 may alter the prodn. of APP and the deposition of βlA4 in the brains of AD patients. Cholinomimetics might slow disease progression through this action.

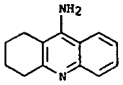
L11 ANSWER 95 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:528788 HCAPLUS
DOCUMENT NUMBER: 122:256428
TITLE: Composition and method using **acetylcholine** agonist and **muscarinic** antagonist for treating nicotine craving in smoking cessation
INVENTOR(S): Callaway, Enoch
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9507690	A1	19950323	WO 1994-US10328	19940913
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5480651	A	19960102	US 1994-213111	19940315
PRIORITY APPLN. INFO.:			US 1993-121606 A	19930915
			US 1994-213111 A	19940315
			US 1992-851914 B2	19920316

AB A method for relieving craving in a nicotine-habituated patient and a composition for treating the patient is provided. The composition administered has a nonspecific **acetylcholine** agonist and a **muscarinic** antagonist. A particularly preferred composition for relieving craving takes the form of a tablet where the first component is a water-soluble physostigmine and the second component is a water-soluble scopolamine. Patients treated have reported a slight increase in alertness and a diminished craving for nicotine.

IT **321-64-2**, Tacrine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**acetylcholine** agonist and **muscarinic** antagonist for treating nicotine craving in smoking cessation)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

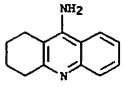


L11 ANSWER 96 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:522364 HCAPLUS
DOCUMENT NUMBER: 122:282108
TITLE: Antagonism of scopolamine-induced memory impairments in rats by the **muscarinic** agonist RU 35 926 (CI-979)
AUTHOR(S): M'Harzi, M.; Palou, A.-M.; Oberlander, C.; Barzaghi, F.
CORPORATE SOURCE: Pharmacol. Effets Centraux, Centre Rech. Roussel UCLAF, Romainville, 93235, Fr.
SOURCE: Pharmacology, Biochemistry and Behavior (1995), 51(1), 119-24
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The promnesic effects of RU 35 926 (CI-979), a **muscarinic** receptor agonist, were evaluated on memory impairments induced by the **muscarinic** antagonist scopolamine, using a radial arm maze task, in comparison with tetrahydroaminoacridine (THA), a cholinesterase inhibitor. Groups of rats were trained in a standard version of the radial maze until they had attained an asymptotic level of performance. The animals were then retested with 1 trial a day. Twenty minutes before each retest, the rats were given s.c. administration of 0.1 mg scopolamine/kg. Oral administration of RU 35 926 (0.02, 0.05, 0.1, 0.2, and 0.5 mg/kg) 30 min before the memory retest markedly reduced or suppressed the scopolamine-induced deficit. This reduction was evidenced by a decrease in the different types of errors and an increase in the number of correct responses. THA (3 mg/kg, i.p. or orally) given 20 min prior to testing also reduced or suppressed the scopolamine-induced deficits. These results show that RU 35 926 possesses the capacity to reduce memory impairments induced by a deficit of cholinergic transmission in the rat.

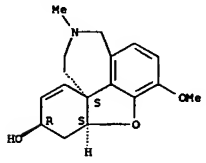
IT **321-64-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antagonism of scopolamine-induced memory impairment by the **muscarinic** agonist RU 35926 and tetrahydroaminoacridine)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 97 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:386966 HCAPLUS
DOCUMENT NUMBER: 122:204920
TITLE: Non-specific effects of some cholinopositive and anticholinergic drugs in toxic doses
AUTHOR(S): Krylov, S.S.; Semenov, E.V.; Suchovskaja, T.A.
CORPORATE SOURCE: Laboratory of Biochemical Pharmacology, Institute of Toxicology, Leningrad, Russia
SOURCE: Current Toxicology (1993), 1(3/4), 239-42
CODEN: CUTOEX; ISSN: 1069-4587
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Muscarinic cholinolytics cause different memory and behavior disorders as well as motor excitation, tachycardia, arterial hypertension in toxic doses. The last three symptoms are manifestations of syzpathetic nervous system hyperactivity. The authors showed that muscarinic cholinolytics cause motor excitation and increased Ca2+ and phosphoinositides metabolism in brain synaptosomes. As a result many different mediators are released from nerve terminals into their synaptic clefts. The "Mediator chaos" may cause unregulated excitation and inhibition processes in the CNS. Central nicotinic, muscarinic cholinolytics do not cause such effects. They cause inhibitory effects only, including psychomotor inhibition. Cholinopos. drugs cause cholinergic excitation.
IT 1953-04-4, Nivaline
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(non-specific effects of some cholinomimetics and anticholinergic drugs in toxic doses on calcium and phosphoinositides of brain)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

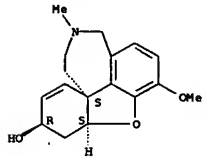


● HBr

L11 ANSWER 98 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:369321 HCAPLUS
DOCUMENT NUMBER: 122:151167
TITLE: Influence of Nivalin P on the training and memorizing processes in rats
AUTHOR(S): Markov, Marko; Danchev, Nikolai; Uzunov, Petko; Higashino, Hideaki; Suzuki, Aritomo
CORPORATE SOURCE: Higher Medical School, Faculty Medicine, Sofia, 1431, Bulg.
SOURCE: Acta Medica Kinki University (1994), 19(2), 119-26
CODEN: AMKUDT; ISSN: 0386-6092
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of Nivalin P (Galanthamine (Nivalin) and 4-aminopyridine (Pymadine) in combination ratio of 1:1) on the total latency time, conditional, unconditional and inadequate reactions in rats were studied. Nivalin is a cholinesterase inhibitor which enhances the cholinergic system by blocking the degradation of the mediator acetylcholine (ACh) in the synapse. Pymadine is a stimulator of the presynaptic release of ACh and its synthesis. The expts. were performed with male Wistar rats weighing 150-170 g which were divided into 4 groups: control and three exptl. groups treated orally with Nivalin P in a dose of 6.6 mg/kg (= 1/5 LD50), 3.3 mg/kg (= 1/10 LD50) and 1.65 mg/kg (= 1/20 LD50), resp. A two-way active avoidance method in a "shuttle box" and the method of Valcelli, L. were used for examination of the memory traces. Nivalin P applied
in a dose 1/20 of the LD50 orally in rats facilitates the training of rats and improves the memory capabilities decreasing the number of inadequate replies. These findings indicate that Nivalin P in low doses induces the enhancement of the cholinergic activity by pharmacol. intervention within the synapse. Apparently, the role of combination therapies, including inhibitors of the breakdown of ACh with facilitators of neuronal calcium uptake appears logical and might be useful in the treatment of Alzheimer's disease.
IT 1953-04-4, Nivalin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nivalin/pymadine combination effect on training and memorizing processes in relation to Alzheimer's disease treatment)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

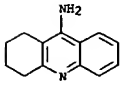
Absolute stereochemistry. Rotation (-).

L11 ANSWER 98 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



● HBr

L11 ANSWER 99 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:284294 HCAPLUS
DOCUMENT NUMBER: 122:48717
TITLE: The neuroprotective effect of tacrine on trimethyltin induced memory and muscarinic receptor dysfunction in the rat
AUTHOR(S): O'Connell, Alan; Earley, Bernadette; Leonard, B. E.
CORPORATE SOURCE: Pharmacology Dep., Univ. College, Galway, Ire.
SOURCE: Neurochemistry International (1994), 25(6), 555-66
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study chronic (39 days) tacrine (3 mg/kg i.p.) treatment significantly improved trimethyltin (8 mg/kg i.p.) induced deficits in spatial navigation. Tacrine also reduced trimethyltin induced hyperactivity and passive avoidance deficits but these effects did not reach statistical significance. The effect of trimethyltin on muscarinic (M1 and M2) receptor sites was determined by means of quant. autoradiog. using [3H]quinuclidinyl benzilate. A selective pattern of M1 and M2 receptor loss was observed mainly affecting the hippocampus and other limbic structures while leaving other brain regions intact. Tacrine successfully prevented the M1 and M2 receptor loss in the CA1 and CA4 hippocampal subfields. The improvement in trimethyltin behavioral toxicity following tacrine treatment may be related to the protective effect of this compound on muscarinic receptor d. in the hippocampal formation and lends support to the hypothesis that cholinergic system dysfunction may be primarily responsible for trimethyltin induced deficits in cognitive function.
IT 321-64-2, Tacrine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neuroprotective effect of tacrine on trimethyltin induced memory and muscarinic receptor dysfunction in brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

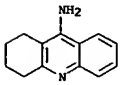


L11 ANSWER 100 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:277712 HCAPLUS
DOCUMENT NUMBER: 122:71791
TITLE: MKC-231, a choline uptake enhancer, ameliorates working memory deficits and decreased hippocampal acetylcholine induced by ethylcholine aziridinium ion in mice
AUTHOR(S): Murai, S.; Saito, H.; Abe, E.; Masuda, Y.; Odashima, J.; Itoh, T.
CORPORATE SOURCE: School of Dentistry, Iwate Medical University, Morioka, Japan
SOURCE: Journal of Neural Transmission: General Section (1994), 98(1), 1-13
CODEN: JNGSEB; ISSN: 0300-9564
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of acute and chronic administration of MKC-231, a new choline uptake enhancer, and two other nootropic agents, linopiridine (Dup 996) and tetrahydroaminoacridine (THA) on working memory deficits and decreased hippocampal acetylcholine (ACh) content were studied in a delayed non-matching to sample task, using a T-maze, in ethylcholine aziridinium ion (AF64A)-treated mice. Treatment with AF64A (3.5 nmol, i.c.v.) produced memory deficits and decreased hippocampal ACh content. In acute behavioral expts., MKC-231 and THA had no significant effect on AF64A-induced memory deficits at any doses tested (0.3, 1.0 and 3.0 mg/kg), whereas Dup 996, at a dose of 1.0 mg/kg, significantly improved memory deficits. In chronic expts., MKC-231 improved memory deficit at all doses tested (0.3, 1.0, or 3.0 mg/kg p.o., once daily for 11 days) and Dup 996 did so only at a dose of 3.0 mg/kg, whereas THA did not improve memory deficit at any doses tested. In acute neurochem. expts., MKC-231 and THA did not reverse the AF64A-induced hippocampal ACh depletion. Dup 996, however, further decreased hippocampal ACh content compared to that in the AF64A-treated group. In chronic expts., MKC-231 significantly reversed hippocampal ACh depletion at doses of 0.3 and 1.0 mg/kg, whereas neither Dup 996 nor THA reversed hippocampal ACh depletion at any doses tested. These results indicate that MKC-231 improved the AF64A-induced working memory deficit and hippocampal ACh depletion, probably by recovering reduced high-affinity choline uptake and ACh release.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linopiridine effect on working memory deficits and decreased hippocampal acetylcholine induced by ethylcholine aziridinium ion in mice)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

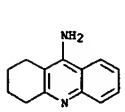


L11 ANSWER 101 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:256865 HCAPLUS
DOCUMENT NUMBER: 122:46298
TITLE: Allosteric effects of the alkane-bis-ammonium compound W84 and of tacrine on [3H]pirenzepine binding at M1-receptors in rat cerebral cortex
AUTHOR(S): Mohr, Klaus; Traenkle, Christian
CORPORATE SOURCE: Inst. of Pharmacy, Univ. Bonn, Bonn, D-53121, Germany
SOURCE: Pharmacology & Toxicology (Copenhagen) (1994), 75(6), 391-4
CODEN: PHTOEH; ISSN: 0901-9928
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bis-quaternary W84, hexamethylene-bis-[dimethyl-(3-phthalimidopropyl)ammonium bromide], is a potent allosteric modulator of M2-cholinoceptors. In this study, the authors aimed at quantifying its allosteric effect on the dissociation of [3H]pirenzepine from M1-cholinoceptors in rat cerebral cortex and to measure the effects on association and equilibrium binding of [3H]pirenzepine. For sake of comparison, tacrine was included which is known to be a potent allosteric modulator of [3H]pirenzepine binding to M1-receptors. Under control conditions (3 mM MgHPO4, 50 mM Tris-HCl, pH 7.4, 23°), [3H]pirenzepine binding was characterized by KD = 5 nM and Bmax = 965 fmol/mg membrane protein, the rate consts. amounting to k+1 = 5.0 μM-1 + min-1 and k-1 = 0.031 min-1. W84 and tacrine reduced [3H]pirenzepine binding concentration-dependently with IC50-values of 1.9 μM and 2.6 μM, resp. [3H]pirenzepine association was inhibited by the compds. with EC50,ass = 1.8 μM for W84 and EC50,ass = 2.4 μM for tacrine. The concentration reducing the dissociation rate by 50% amounted to EC50,diss = 21 μM for W84 and to EC50,diss = 54 μM for tacrine. Compared with W84, the dose-response curves of tacrine for the investigated effects were significantly steeper. In conclusion, W84 affected [3H]pirenzepine binding to M1-receptors allosterically with a higher potency than tacrine but probably by a different mechanism.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(allosteric effects of alkane-bis-ammonium compound W84 and of tacrine on [3H]pirenzepine binding at muscarinic M1-receptors in rat cerebral cortex)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



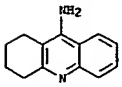
L11 ANSWER 102 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:251679 HCAPLUS
DOCUMENT NUMBER: 122:23741
TITLE: Effects of the centrally acting cholinesterase inhibitors tetrahydroaminoacridine and E2020 on the basal concentration of extracellular acetylcholine in the hippocampus of freely moving rats
AUTHOR(S): Kawashima, Koichiro; Sato, Akio; Yoshizawa, Masayuki; Fujii, Takeshi; Fujimoto, Kazuko; Suzuki, Takeshi
CORPORATE SOURCE: Dep. Pharmacoloty, Kyoritsu Coll. Pharmacy, Tokyo, 105, Japan
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1994), 350(5), 523-8
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of the centrally acting cholinesterase (ChE) inhibitors, tetrahydroaminoacridine (THA) and E2020 (1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methylpiperidine hydrochloride), potential drugs for the treatment of senile dementia, on the basal extracellular acetylcholine (ACh) concentration in the hippocampus of freely moving rats, were determined using a microdialysis technique without the use of a ChE inhibitor in the perfusion fluid and a sensitive RIA. The mean (±SEM) basal ACh content in the perfusate was 103.1 fmol/sample collected over 30 min when microdialysis probes with a length of 3 mm dialysis membrane were used. The content of ACh decreased to an almost undetectable level upon perfusion of magnesium, suggesting that, in the present study, most of the ACh detected in the perfusates was due to cholinergic neuronal activity. THA (1.65 mg/kg, i.p.) produced an insignificant increase in the extracellular ACh concentration, but a dose of 5 mg/kg, i.p. caused a prolonged and significant 5.5-fold increase from the control value. E2020 (0.65 and 2 mg/kg, i.p.) produced significant, prolonged and dose-dependent increases (4 and 12 times the control value, resp.), the peak effect occurring within 1 h. Perfusion with 10 μmol/l physostigmine produced an about 30-fold increased of ACh output, suggesting that the basal extracellular ACh concentration is highly dependent on ChE activity. When ChE was inhibited locally by perfusion with physostigmine, THA (5 mg/kg) produced a transient and, at its maximum, a 1.42-fold increase in extracellular ACh concentration These result demonstrate that the basal, physiol., extracellular ACh concentration in the hippocampus of freely moving rats can be determined using a microdialysis technique and a sensitive RIA, and suggest that THA and E2020 increase ACh concentration in the synaptic cleft of the hippocampus in a dose-dependent manner mostly through ChE inhibition.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of centrally acting cholinesterase inhibitors tetrahydroaminoacridine and E2020 on basal concentration of extracellular acetylcholine in hippocampus of freely moving rats)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 102 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 103 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

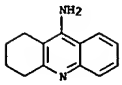
ACCESSION NUMBER: 1995:231924 HCAPLUS
DOCUMENT NUMBER: 122:23649
TITLE: Characterization of a novel muscarinic receptor agonist, YM796: comparison with cholinesterase inhibitors in in vivo pharmacological studies
AUTHOR(S): Wanibuchi, Fumikazu; Nishida, Takako; Yamashita, Hiroshi; Hidaka, Kazuyuki; Koshiya, Kazuo; Tsukamoto, Shin-ichi; Usuda, Shinji
CORPORATE SOURCE: Neuroscience and Gastrointestinal Laboratories, Yamanouchi Institute for Drug Discovery Research, 21 Miyukigaoka, Tsukuba, Ibaraki, 305, Japan
SOURCE: European Journal of Pharmacology (1994), 265(3), 151-8
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous reports have shown that (±)-YM796 (2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]decane) exhibits M1 agonistic activity and ameliorates cognitive impairment, and that the (-)-S isomer is active in in vitro studies. The authors report here the characterization of the (-)-S isomer, YM796 ((-)-(S)-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]decane L-tartrate monohydrate), and its (+)-R isomer in in vivo pharmacol. studies in comparison with the cholinesterase inhibitors tacrine, amiridine and E-2020. YM796 (0.031-0.5 mg/kg p.o.), like the racemate, reversed the cognitive impairment in passive avoidance tasks of rats with nucleus basalis magnocellularis lesions, whereas (+)-R-YM796 was ineffective in this exptl. amnesia. YM796 exhibited only weak effects on mouse salivation and hypothermia, a peripheral cholinergic response and a central cholinergic response, resp. The (+)-R isomer, however, failed to induce these cholinergic responses. YM796 also ameliorated the memory deficits induced by scopolamine in rats and electroconvulsive shock in mice. The potency of YM796 in these exptl. amnesia models was over 100 times greater than that of tacrine, over 10 times greater than that of E-2020, and 6 times greater than that of amiridine. In salivary secretion and hypothermia, YM796 was 2-4 times weaker than tacrine and E-2020, and 1-2 times stronger than amiridine. Thus, YM796's ratio of anti-amnesic effects to salivary secretion and hypothermia was much greater than that of the cholinesterase inhibitors tested. Taken together with previous data which show that YM796, but not its (+)-R isomer, possesses M1 agonistic activity, the difference between YM796 and the (+)-R isomer in anti-amnesic effects suggests that YM796 ameliorates cognitive impairment through, at least in part, the activation of central muscarinic M1 receptors. Moreover, the fact that YM796 is more selective for anti-amnesic effects than other cholinergic responses may be due to its selectivity and efficacy for specific muscarinic receptor subtypes, predominantly for the M1 subtype.

IT 1684-40-8, Tacrine hydrochloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of novel muscarinic receptor agonist YM796 and comparison with cholinesterase inhibitors in in vivo pharmacol. studies)

RN 1684-40-8 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-, monohydrochloride (9CI) (CA INDEX

L11 ANSWER 103 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
NAME)



● HCl

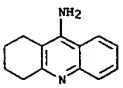
L11 ANSWER 104 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:223831 HCAPLUS
DOCUMENT NUMBER: 122:939
TITLE: Effect of NIK-247 on basal concentrations of extracellular acetylcholine in the cerebral cortex of conscious, freely moving rats
AUTHOR(S): Ishii, Yutaka; Kojima, Jun; Ikeda, Naoko; Kawashima, Koichiro
CORPORATE SOURCE: Division of Pharmacology, Omiya Research Laboratory, Nikken Chemicals Co., Ltd., Saitama, 330, Japan
SOURCE: Japanese Journal of Pharmacology (1994), 66(3), 289-93
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We studied the effect of orally administered NIK-247 (9-amino-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]quinoline monohydrochloride monohydrate) on basal extracellular acetylcholine (ACh) concns. in the rat cerebral cortex using microdialysis without the addition of cholinesterase inhibitor to the perfusion fluid and RIA for ACh. In addition, the effect of oral administration of NIK-247 on acetylcholinesterase (AChE) activity in rat cerebral cortex was determined The mean basal ACh content in the perfusate from the cerebral cortex of freely moving rats was 123.2±21.8 fmol/30 min (n=7). NIK-247 (2.5-10.0 mg/kg, p.o.) increased the ACh content of the perfusate in a dose-dependent manner. NIK-247 at 10 mg/kg significantly increased the ACh content in the perfusate from 0.5 to 2.5 h after administration, and the maximum increase was attained at 1 h after administration. 9-Amino-1,2,3,4-tetrahydroacridine (5 mg/kg, p.o.) and physostigmine (0.5 mg/kg, i.p.) significantly increased the ACh content in the perfusate from 1 to 2 h and from 0.5 to 1.5 h after administration, resp. AChE activities in the cerebral cortex were about 32% and 12% below the control value at 1 h and 3 h after administration of NIK-247 at 10 mg/kg, resp. These findings demonstrate that NIK-247 increases extracellular ACh concentration and inhibits AChE activity in the cerebral cortex after oral administration, and they suggest that NIK-247 facilitates central cholinergic transmission.

IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of NIK-247 on basal concns. of extracellular acetylcholine in cerebral cortex)

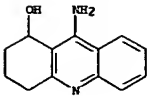
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



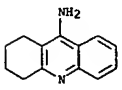
L11 ANSWER 105 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:116986 HCAPLUS
DOCUMENT NUMBER: 122:219
TITLE: Stereoselective hydroxylation of tacrine in rats and humans
AUTHOR(S): Hooper, Wayne D.; Pool, William F.; Woolf, Thomas F.; Gal, Joseph
CORPORATE SOURCE: Dep. Pharmacokinetics Drug Metabolism, Univ. Colorado Sch. Med., USA
SOURCE: Drug Metabolism and Disposition (1994), 22(5), 719-24
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An enantiospecific method was developed for assessing the stereochem. of tacrine (9-amino-1,2,3,4-tetrahydroacridine monohydrochloride monohydrate; THA) metabolism to 1-hydroxytacrine (1-OH-THA) in humans and rats. In addition, limited metabolic studies with human liver microsomal prepns. were conducted, and the stereochem. of rac-1-OH-THA disposition was also examined The anal. method incorporates an achiral normal phase separation and isolation of 1-OH-THA, followed by a chromatog. step using chiral normal-phase chromatog. to resolve the enantiomers of 1-OH-THA. The achiral method was applied to quantitation of total 1-OH-THA in human urine specimens collected for 24 h following administration of a single 40 mg oral dose of tacrine to 15 healthy elderly volunteers. Total 1-OH-THA accounted for .apprx.5% of the administered dose. THA and 2-OH-THA were also quantitated and found to comprise <1% and .apprx.2% of the administered does, resp. 4-OH-THA was not detectable. The dextrorotatory (+)- isomer comprised .apprx.94% of the 1-OH-THA recovered in urine. In vitro studies utilizing human liver microsomes found enantioselective formation of the (+)-isomer (.apprx.90%), whereas incubations with rac-1-OH-THA showed residual substrate to be racemic. The method was also applied to determination of the enantiomeric composition of 1-OH-THA in the urine of rats given a single oral 16 mg/kg dose of THA. The percentage of 1-OH-THA excreted in urine as the (+)-isomer was 94%. Following administration of rac-1-OH-THA to rats (2 mg/kg dose), urinary 1-OH-THA was racemic. Thus, in humans and rats, the metabolism of THA to 1-OH-THA is highly stereoselective, whereas metabolism of 1-OH-THA appears to be nonstereoselective.
IT 121445-24-7
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(stereoselective hydroxylation of tacrine in rats and humans)
RN 121445-24-7 HCAPLUS
CN 1-Acridinol, 9-amino-1,2,3,4-tetrahydro-, (+)- (9CI) (CA INDEX NAME)

Rotation (+).

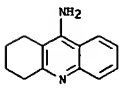
L11 ANSWER 105 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 106 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:652953 HCAPLUS
DOCUMENT NUMBER: 121:252953
TITLE: Role of nitric oxide in the pathophysiology of neurodegeneration induced by tacrine in lithium pretreated rats
AUTHOR(S): Bagetta, Giacinto; Paoletti, A. Maria; Rodino, Paola; Nistico, Giuseppe
CORPORATE SOURCE: Department of Experimental Medicine, University of Reggio, Calabria, Italy
SOURCE: International Academy for Biomedical and Drug Research (1994), 7(Recent Advances in the Treatment of Neurodegenerative Disorders and Cognitive Dysfunction), 125-8
CODEN: IABREE; ISSN: 1019-2069
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors report that in the exptl. model of seizures and brain damage by systemic administration of cholinomimetics in Li+ pretreated animals is preceded by increases in Ca2+-calmodulin-dependent nitric oxide synthase activity and accumulation of cyclic GMP in the hippocampus, thus implicating excessive nitric oxide production in the pathophysiol. A pretreatment with atropin prevented the effects of tacrine thus suggesting that muscarinic acetylcholine receptors are involved.
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nitric oxide role in the pathophysiol. of neurodegeneration induced by tacrine in lithium pretreated rats)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



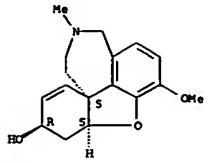
L11 ANSWER 107 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:648193 HCAPLUS
DOCUMENT NUMBER: 121:248193
TITLE: Theoretical and experimental justification of development of new methods for bioidentification of anticholinesterase compounds in an aquatic environment
AUTHOR(S): Tonkopii, V. D.; Kutsenko, S. A.; Zagrebin, A. O.; Sherstneva, L. A.
CORPORATE SOURCE: Inst. Ozeroved., St.-Petersburg, Russia
SOURCE: Zhurnal Ekologicheskoi Khimii (1993), (2), 133-7
CODEN: ZEKHE6; ISSN: 0869-3498
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Cholinergic system of Daphnia magna was examined using anticholinesterase compds. of different classes (reversible inhibitors, organophosphorus compds., carbamates). Central M-cholinolytics decrease the toxicity of armin and aminostigmin. The anticholinesterase compds. enhanced the toxicity of the myorelaxant ditilin. Daphnia magna could be used for identifying different classes of anticholinesterase compds.
IT 321-64-2, Tacrine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bioidentification of anticholinesterase compds. in Daphnia magna)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



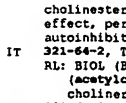
L11 ANSWER 108 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:571172 HCAPLUS
DOCUMENT NUMBER: 121:171172
TITLE: Physostigmine and galanthamine: probes for a novel binding site on the α4β2 subtype of neuronal nictonic acetylcholine receptors stably expressed in fibroblast cells
AUTHOR(S): Pereira, Edna F. R.; Alkondon, Manickavasagom; Reinhardt, Sigrid; Maelicke, Alfred; Peng, Xiao; Lindstrom, Jon; Whiting, Paul; Albuquerque, Edson X.
CORPORATE SOURCE: Sch. Med., Univ. Maryland, Baltimore, MD, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 270(2), 768-78
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, we demonstrated that the chicken α4β2 neuronal nicotinic receptor stably expressed in transfected mouse fibroblasts (M10 cells) can be activated via the acetylcholine -binding site or via a site that is distinct from that for acetylcholine and recognizes physostigmine and galanthamine as agonists. In outside-out patches excised from dexamethasone-induced M10 cells, (+)-anatoxin-a, physostigmine and galanthamine (each at 1 μM) activated single channels with conductances of 18 and 30 pS. Dihydro-β-erythroidine (1-30 nM), but not the nicotinic receptor-specific monoclonal antibody FK1, reduced the frequency of channels activated by anatoxin (1 μM). On the other hand, the frequency of channel activity induced by physostigmine (1 μM) was unaffected by dihydro-β-erythroidine and was markedly decreased by FK1. In uninduced M10 cells and in dexamethasone-treated untransfected fibroblasts, we observed that physostigmine, galathamine and nicotinic agonists did not evoke whole-cell or single-channel currents. Also, neither [3H]L-nicotine nor FK1 was able to bind to uninduced M10 cells. In dexamethasone-induced M10 cells, the nicotinic agonists acetylcholine, anatoxin, 1,1-dimethyl-4-phenylpiperazinium, (-)-nicotine, and cytisine (each at 100 μM) activated whole-cell currents that showed a market inward rectification and were sensitive to blockade by dihydro-β-erythroidine (100 nM). However, neither galanthamine nor physostigmine could evoke whole-cell currents in cells that were responsive to nicotinic agonists. Other effects of physostigmine and galanthamine on the nicotinic receptor that outweigh the agonist properties of these compds. could account for their inability to evoke whole-cell currents.
IT 357-70-0, Galanthamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neuronal nicotinic receptor α4β2 subtype binding site activation by)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 108 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

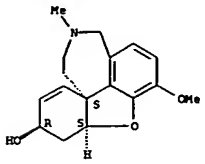


L11 ANSWER 109 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:570421 HCAPLUS
DOCUMENT NUMBER: 121:170421
TITLE: Tacrine increases stimulation-evoked acetylcholine release from rat hippocampal slices
AUTHOR(S): Suzuki, Takeshi; Nonaka, Hikaru; Fujimoto, Kazuko; Kawashima, Koichiro
CORPORATE SOURCE: Dep. Pharmacol., Kyoritsu Coll. Pharm., Tokyo, 105, Japan
SOURCE: Japanese Journal of Pharmacology (1994), 65(4), 337-42
CODEN: JJPAAZ; ISSN: 0021-5198
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examined the effects of tacrine (9-amino-1,2,3,4-tetrahydroacridine) on endogenous acetylcholine (ACh) release from rat hippocampal slices. Tacrine (more than 1 μM) increased the measurable amount of basal ACh release. On the other hand, in the presence of physostigmine (50 μM; under this condition, cholinesterase activity was inhibited), tacrine did not enhance the basal ACh release. Tacrine at more than 100 μM increased the submaximal elec. stimulation-evoked release of ACh in both the absence and presence of physostigmine (50 μM). This effect of tacrine was abolished by a combination of atropine (100 nM) and physostigmine. These results indicate that a high-dose of tacrine increases cholinergic neurotransmission not only by inhibition of cholinesterase but also by increasing ACh release through an atropine-like effect, perhaps by blockade of part of the process of muscarinic autoinhibition.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine release stimulation by, in hippocampus, cholinergic neurotransmission modulation mechanism in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

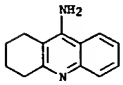


L11 ANSWER 110 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:569637 HCAPLUS
DOCUMENT NUMBER: 121:169637
TITLE: Galanthamine and rat gastrointestinal tract in situ and in vitro.
AUTHOR(S): Yamboliev, I.; Mutafova-Yamblieva, V.; Mihailova, D.
CORPORATE SOURCE: Faculty Pharmacy, Sofia, 1000, Bulg.
SOURCE: European Journal of Drug Metabolism and Pharmacokinetics (1993), (SPEC. ISSUE, PROCEEDINGS OF THE FIFTH EUROPEAN CONGRESS OF BIOPHARMACEUTICS AND PHARMACOKINETICS, 1993), 50-5
CODEN: EJDPD2; ISSN: 0378-7966
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The disappearance kinetics of the acetylcholinesterase inhibitor galanthamine hydrobromide from the gastrointestinal tract of male Wistar rats (200-250 g) in situ have been examined After 30 min the galanthamine loss was 16% in the stomach (pH 2), 54-85% in the duodenum and the successive small intestinal segments (pH 6.8), 43% in the colon and 76% in the rectum. The simple diffusion was considered to be the major transport mechanism because in the proximal jejunum, terminal ileum and rectum the disappearance rate was linearly dependent on the galanthamine dose (range 0.54 mg). Compared to the other segments (0.240.32 + 10-2 mg/cm.min) the disappearance rate was higher in the terminal ileum (0.38 + 10-2 mg/cm.min) and especially in the rectum (1.27 + 10-2 mg/cm.min). This difference was evaluated in vitro. In a dose range 100-300 M (comparable to the in situ dose-range) galanthamine induced increase in the smooth muscle tone and in the spontaneous mech. activity both in the jejunum and ileum, being higher in the latter segment. This increase was significantly reduced by atropine suggesting the major role of the muscarinic part of the cholinergic system. Thus, galanthamine seems to stimulate its own absorption, more intensively in the distal intestinal part. Nevertheless, the results suggest that after oral administration in vivo rapid galanthamine absorption could be expected all over the rat gastrointestinal tract with the site-specific absorption playing an insignificant role. The interest in the biodistribution and pharmacokinetics of the anticholinesterase agent galanthamine has increased in the recent years because of its predicted effectiveness in the treatment of Alzheimer's disease. Different animal species including man have been involved in the pharmacol. and pharmacokinetic study of galanthamine and its metabolites. Previous investigations conducted by authors have shown that following oral administration of galanthamine to rats first-order absorption kinetics is consistent with the plasma concentration-time data with absolute bioavailability about 65%. However, the absorption kinetics in healthy volunteers indicated that the rate of absorption varied along the GI tract and based upon the data a two-stage absorption process was proposed. The aim of the present study was to investigate the rate of loss of galanthamine by different segments of the GIT of the rat in situ and also to assess the relationship between the concentration of galanthamine and the contractile activity of some GIT segments in vitro.
IT 357-70-0, Galanthamine
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(contractile activity and pharmacokinetics of acetylcholinesterase inhibitor galanthamine hydrobromide in gastrointestinal tract)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

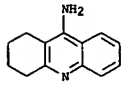
L11 ANSWER 110 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry. Rotation (-).



L11 ANSWER 111 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:524963 HCAPLUS
DOCUMENT NUMBER: 121:124963
TITLE: Modulation of activity and plasticity of cholinoreceptors on the neurons of a snail by amiridine and tacrine: phenomenon and mechanisms
AUTHOR(S): Burov, Yu. V.; Drozdova, E. I.; Pivovarov, A. S.; Robakidze, T. N.
CORPORATE SOURCE: Natl. Res. Cent. Safety Biol. Active Compds., Staraya Kupavna, Russia
SOURCE: Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova (1993), 43(6), 1202-9
CODEN: ZVNDAM; ISSN: 0044-4677
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The effects of amiridine and tacrine on the membrane potential, activity, and plasticity of cholinoreceptors have been studied using the recording of intracellular and transmembrane currents in identified neurons of Helix lucorum. Amiridine and tacrine (1-100 mM) have no noticeable effects on the membrane potential of the cells. Both compds. modulate the activity of cholinoreceptors judging from their influence on the inward current induced by local acetylcholine (ACh) application: they increase the duration of the current with a two-phase effect on the amplitude (a short-latent intensification with a following decrease). Amiridine and tacrine intensify ACh current extinction induced by repeated ACh application to the soma. Acetylcholinesterase inhibitor physostigmine has a similar modulating effect on ACh current and its extinction. It impedes the modulating effects of amiridine and tacrine. Amiridine and physostigmine directly affect cholinoreceptors and ion channels controlled by them changing in a similar way the current-voltage curves of ACh-current and approximating it to the equilibrium potential of chloride ions.
Modulating effects of amiridine, tacrine and physostigmine on the activity and plasticity of cholinoreceptors may be supposed to be caused by their direct membrane-cytoplasmic action.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(neuron cholinoreceptor activity modulation by, direct membrane-cytoplasmic activity and pharmacol. action in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

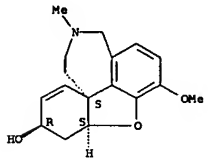


L11 ANSWER 112 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:498827 HCAPLUS
DOCUMENT NUMBER: 121:98827
TITLE: Test unit for detection of trace amounts of organophosphorus pesticides and pharmaceutical preparations of anti-choline esterase action
AUTHOR(S): Nikol'skaya, E. B.; Evtyugin, G. A.; Svyatkovskii, A. V.; Iskanderov, R. R.; Suntsov, E. V.; Prokopov, A. A.; Moralev, S. N.; Kormilitsin, B. N.; Latypova, V. Z.
CORPORATE SOURCE: I. M. Sechenov Inst. Evol. Physiol. Biochem., St. Petersburg, Russia
SOURCE: Zhurnal Analiticheskoi Khimii (1994), 49(4), 374-80
CODEN: ZAKHA8; ISSN: 0044-4502
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB A test unit from solid solns. of choline esterase in N-phthalylchitosane was developed for the detection of trace substances of anti-choline esterase action in H2O, corn and meat. The detection limits for the organophosphorus pesticides studied are 0.0015-0.3 μg/mL. The possibility was shown of the detection of the compds. of anti-choline esterase action in meat and plant samples. The test unit may be recommended for use in field and laboratory studies as a means of primary control of contamination of the environment by pesticides of anti-choline esterase action.
IT 321-64-2, Tacrine
RL: ANST (Analytical study)
(determination of trace, using photometric analyzer)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 113 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:449906 HCAPLUS
DOCUMENT NUMBER: 121:49906
TITLE: In vivo selectivity in the action of muscarinic agonists
AUTHOR(S): Kosmachev, A. B.; Kosmacheva, I. M.; Yankhotova, M. B.; Kuleshov, V. I.
CORPORATE SOURCE: Inst. Toxicol., St. Petersburg, 193019, Russia
SOURCE: Eksp. Klin. Farmakol. (1994), 57(2), 6-8
CODEN: EKFAE9; ISSN: 0869-2092
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Expts. on inhibition of tremor reaction induced by various cholinomimetics have established that DED50 of atropine and amedine is significantly indifferent when tremor is caused by pilocarpine, oxotremorine, and aceclidine while the activity of amedine is lower than that of atropine when ezerin, arecoline, and galantamine are applied. The comparison of the findings with the data on the selectivity of the above M-cholinolytics leads to the conclusion that, in in vivo expts., the muscarinic agonists are able to show their selectivity against various subtypes of M-cholinoreceptors. The results of in vivo expts. are found to differ from the data on the in vitro selectivity of M-cholinomimetics in some cases.
IT 357-70-0, Galantamine
RL: BIOL (Biological study)
(in vivo selectivity of, as muscarinic agonist)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

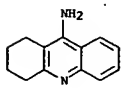


L11 ANSWER 114 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:315694 HCAPLUS
DOCUMENT NUMBER: 120:315694
TITLE: Tacrine-induced increase in the release of spontaneous high quantal content events in Torpedo electric organ
AUTHOR(S): Canti, Carles; Marti, Eulalia; Marsal, Jordi; Solsona, Carles
CORPORATE SOURCE: Fac. Med., Univ. Barcelona, Barcelona, E-08013, Spain
SOURCE: British Journal of Pharmacology (1994), 112(1), 19-22
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

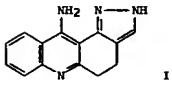
AB The anticholinesterases, tacrine (100 μM) and physostigmine (60 μM) had different effects on the amplitude distribution and kinetics of miniature endplate currents (m.e.p.cs) recorded extracellularly from the elec. organ of Torpedo marmorata. Tacrine increased the ratio of giant miniatures (larger than 4 mV of amplitude) to more than 20% of recorded spontaneous events. In the presence of physostigmine such events represented only 4%. Both tacrine and physostigmine increased the rise time and the decay phase of normal-sized m.e.p.cs when compared to control conditions. Both effects were significantly greater for tacrine. The authors have tested the specificity of the tacrine effect on ectoenzyme activities associated with plasma membranes of these pure cholinergic nerve endings. Tacrine does not act unspecifically on every ectoenzyme, because it is not able to block the ectoapyrase activity even at a concentration 100 fold greater than that required to inhibit 94% of AChE. The authors conclude that the differential effects of tacrine and physostigmine can be explained in terms of undetd. presynaptic actions of tacrine, while comparable effects of the two compds. can be explained through a shared anticholinesterase activity.

IT **321-64-2**, Tacrine
RL: BIOL (Biological study)
(spontaneous high quantal content events release in Torpedo elec. organ induction by physostigmine vs., mechanism of)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 115 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:217580 HCAPLUS
DOCUMENT NUMBER: 120:217580
TITLE: Synthesis of some amino-4,5-dihydropyrazolol[3,4-a]acridines as potential cholinesterase inhibitors
AUTHOR(S): Shutske, Gregory M.; Tomer, John D., IV
CORPORATE SOURCE: Hoechst-Roussel Pharm. Inc., Somerville, NJ, 08876, USA
SOURCE: Journal of Heterocyclic Chemistry (1993), 30(1), 23-7
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



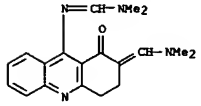
I

AB A preparation of the 4,5-dihydro derivs. of the previously known pyrazolo[3,4-a]acridine ring system is described. The reaction of a 3,4-dihydroacridin-1(2H)-one with DMF di-Me acetal gave a reactive enamino ketone, which yielded the desired heterocycle upon reaction with hydrazine. Using this chemical, 11-amino-4,5-dihydro-2H-pyrazolo[3,4-a]acridine (I) and a number of its 2-substituted derivs. were prepared and evaluated as **acetylcholine** esterase inhibitors, based on their relationship to 1,2,3,4-tetrahydro-9-acridinamine (THA). 1-Amino-4,5-dihydro-1H-pyrazolo[3,4-a]acridine and 2-amino-4,5-dihydrol-1H-pyrazolo[3,4-a]acridine were also prepared and studied as potential cholinesterase inhibitors. All the compds. prepared in this work were tested as cholinesterase inhibitors (sic) but they were found relatively weak (IC50 >20 μM).

IT **153488-72-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation as intermediate for aminodihydropyrazolol[3,4-a]acridine **acetylcholine** esterase inhibitor)

RN 153488-72-3 HCAPLUS
CN Methanimidamide, N'-[2-[(dimethylamino)methylene]-1,2,3,4-tetrahydro-1-oxo-9-acridinyl]-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

L11 ANSWER 115 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



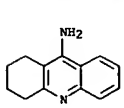
● HCl

L11 ANSWER 116 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:125652 HCAPLUS
DOCUMENT NUMBER: 120:125652
TITLE: Effects of tetrahydroaminoacridine on nicotinic **acetylcholine** receptors: studies at macroscopic and single-channel levels
AUTHOR(S): Edge, Mark Thomas
CORPORATE SOURCE: Univ. Alabama, Birmingham, AL, USA
SOURCE: (1992) 131 pp. Avail.: Univ. Microfilms Int., Order No. DA9302467
From: Diss. Abstr. Int. B 1993, 53(9), 4521
DOCUMENT TYPE: Dissertation
LANGUAGE: English

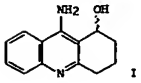
AB Unavailable

IT **321-64-2**, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: BIOL (Biological study)
(nicotinic receptor interaction with)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



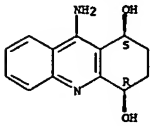
L11 ANSWER 117 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:124019 HCAPLUS
DOCUMENT NUMBER: 120:124019
TITLE: Disposition of [14C]velnacrine maleate in rats, dogs, and humans
AUTHOR(S): Turcan, R. G.; Hillbeck, D.; Hartley, T. E.; Gilbert, P. J.; Coe, R. A. J.; Troke, J. A.; Vose, C. W.
CORPORATE SOURCE: Hoechst Pharm. Res. Lab., Hoechst UK Ltd., Walton/Milton Keynes, MK7 7AJ, UK
SOURCE: Drug Metabolism and Disposition (1993), 21(6), 1037-47
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

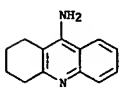
AB This study describes the disposition of 14C-labeled velnacrine (I) maleate in rats, dogs, and humans, and the isolation and identification of metabolites in dog urine. Following oral administration of [14C]velnacrine maleate, drug-related material was well absorbed in all three species, with the majority of the dose recovered in the urine. Fecal elimination of radioactivity accounted for the remainder of the dose. The majority of the radioactivity was eliminated within 24 h. Pharmacokinetic parameters for the elimination of radioactivity from the plasma of rats and dogs were similar after oral dosing compared with i.v. dosing. In humans, the plasma and urinary levels of velnacrine maleate were substantially lower, and the elimination half-life shorter than for total radioactivity, indicating the presence of one or more metabolites with a longer half-life than the parent compound Preliminary TLC anal. of urine, plasma, and feces showed that metabolism appeared to be similar in the three species investigated. Velnacrine maleate was extensively metabolized with only .apprx.10%, 19%, and 33% of the dose appearing in the urine as unchanged drug in humans, dogs, and rats, resp. Isolation and identification of dog urinary metabolites was conducted. The identity of the isolated metabolites was determined by GC/MS and proton NMR. One of the main metabolic routes was found to be via hydroxylation of the tetrahydroaminoacridine ring with other minor hydroxylated and dihydroxylated metabolites being detected. In addition two dihydrodiol metabolites were also identified. Phase II metabolism did not appear to be a significant route.
IT 148932-95-0, cis-4-Hydroxyvelnacrine
RL: FORM (Formation, nonpreparative)
(formation of, as velnacrine metabolite)
RN 148932-95-0 HCAPLUS
CN 1,4-Acridinediol, 9-amino-1,2,3,4-tetrahydro-, cis- (9CI) (CA INDEX NAME)

L11 ANSWER 117 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Relative stereochemistry.



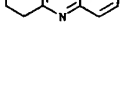
L11 ANSWER 118 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:98683 HCAPLUS
DOCUMENT NUMBER: 120:98683
TITLE: Protection by tacrine and some adjuncts against the depressant effects of soman in guinea pig atrium
AUTHOR(S): Lau, Wai Man
CORPORATE SOURCE: Mater. Res. Lab., Def. Sci. and Technol. Organ., Ascot Vale, 3032, Australia
SOURCE: General Pharmacology (1993), 24(6), 1513-19
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neg. inotropic effects of soman have been reported previously. It was suggested that the depression in atrial force of contraction was a consequence of continuous muscarinic receptor activation by excessive acetylcholine (ACh) accumulation and also possibly through direct interactions at the receptor-associated K+ channels by organophosphate (OP). In this study, the protective effects of tacrine (THA), an antimuscarinic as well as a K+ channel blocker, against soman in guinea-pig atrium were investigated. It was found that tacrine could antagonize the neg. inotropic effects of soman. This antagonism occurred in a concentration-dependent manner, with effective concns. (ECs) for tacrine ranging from 1.7 to 12.1 μM when the atrium was equilibrated with 0.05-10 μM soman. Inclusion of an oxime HI-6 (100 μM) in the regimen improved the efficacy of tacrine against soman (1 μM) by 16.1 fold. Addition of a potent antimuscarinic, either atropine or glycopyrrolate with tacrine, also improved tacrine's efficacy against soman significantly. Atropine, at equivalent concentration, appeared to be the most effective of the three. At 0.1 μM concentration, atropine was 4.25 and 3.47 times more potent than HI-6 and glycopyrrolate, resp., in enhancing THA efficacy. The results suggest that the immediate suppression of the muscarinic manifestations and the reactivation of the enzyme acetylcholinesterase for the removal of excess ACh are both critical in maintaining the mech. functions of a heart during acute OP poisoning. The blockade of K+ channels by tacrine may also contribute to countering the depressant effects of soman.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(soman depressant effect on heart atrium protection by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

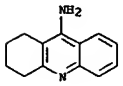


L11 ANSWER 119 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:95653 HCAPLUS
DOCUMENT NUMBER: 120:95653
TITLE: Tetrahydroaminoacridine and physostigmine increase cerebral glucose utilization in specific cortical and subcortical regions in the rat
AUTHOR(S): Bassant, M. H.; Jazat, F.; Lamour, Y.
CORPORATE SOURCE: U 161, INSERM, Paris, 75014, Fr.
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1993), 13(5), 855-64
CODEN: JCBMDN; ISSN: 0271-678X
DOCUMENT TYPE: Journal
LANGUAGE: English

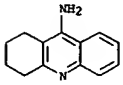
AB The effects of the anticholinesterases tetrahydroaminoacridine (THA) and physostigmine on local cerebral glucose utilization (LCGU) were studied in the conscious rat, using the autoradiog. [14C]deoxyglucose technique. THA (5 mg/kg i.p.) increased LCGU significantly in 8 of the 43 regions studied. A higher dose of THA (10 mg/kg) produced a metabolic activation in 19 of the 43 regions. LCGU increased in cortical areas (including parietal and temporal cortices), the septohippocampal system, the thalamus, the lateral habenula, the basolateral amygdala, the superior colliculus, and the substantia nigra. Scopolamine (4 mg/kg i.p.) reversed the THA-induced LCGU increase. Physostigmine (0.2 and 0.5 mg/kg) increased LCGU in 15 and 22 regions, resp. The average magnitude of the change induced by 0.5 mg/kg of physostigmine was similar to that observed after THA at 10 mg/kg, but the topog. of the effects was somewhat different. Physostigmine increased LCGU in the preoptic magnocellular area, the brainstem, and the cerebellum but not in the parietal cortex. The effects in the septohippocampal system were smaller than those induced by THA. The regional topog. of the LCGU increase overlapped the distribution of the M2 muscarinic receptors and that of acetylcholinesterase activity. These data suggest that the major effects of THA and physostigmine on LCGU result from their anticholinesterase action.
IT 321-64-2, Tetrahydroaminoacridine
RL: BIOL (Biological study)
(cerebral glucose utilization in cortical and subcortical region increase by, anticholinesterase action in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



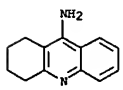
L11 ANSWER 120 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:69390 HCAPLUS
DOCUMENT NUMBER: 120:69390
TITLE: Tetrahydroaminoacridine increases m3-, but not m2-, muscarinic acetylcholine receptor mRNA levels in differentiating cerebellar granule cells
AUTHOR(S): Sunaga, Katsuyoshi; Chuang, De Maw; Ishitani, Ryoichi
CORPORATE SOURCE: Group Cell. Neuropharmacol., Josai Univ., Sakado, 350-02, Japan
SOURCE: Neuroscience Letters (1993), 163(1), 27-30
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors used Northern blot hybridization to determine 9-amino-1,2,3,4-tetrahydroacridine (THA), a potential antidementia drug, selectively altered the levels of muscarinic acetylcholine receptor (mAChR) mRNA in differentiating cerebellar granule cells. Granule cells were cultured for 8 days in media containing 15 mM K+, 25 mM K+ or 15 mM K+ plus 30 μM THA. High K+ markedly increased the levels of m2- and m3-mAChR mRNA in the surviving cells. In contrast, THA increased the levels of m3-mAChR mRNA, but had little or no effect on m2-mAChR mRNA levels. These results suggest that THA selectively up-regulates the synthesis of m3-mAChR mRNA.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(muscarinic receptor mRNA levels selective increase by, in differentiating cerebellar granule cells)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 121 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:662395 HCAPLUS
DOCUMENT NUMBER: 119:262395
TITLE: Similar ameliorating effects of benzomorphans and 5-HT2 antagonists on drug-induced impairment of passive avoidance response in mice: Comparison with acetylcholinesterase inhibitors
AUTHOR(S): Matsuno, K.; Senda, T.; Matsunaga, K.; Mita, S.; Kaneto, H.
CORPORATE SOURCE: Cent. Res. Lab., Santen Pharm. Co., Osaka, 533, Japan
SOURCE: Psychopharmacology (Berlin, Germany) (1993), 112(1), 134-41
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mice were trained to avoid elec. shocks by means of step-down type passive avoidance learning tasks, and memory retention was measured 24 h after the training session. Memory impairment (amnesia) was produced by administering either p-chloroamphetamine (PCA), a serotonin (5-HT) releaser or scopolamine (SCOP), a muscarinic cholinoceptor antagonist, 30 min prior to the training session. Benzomorphans, 5-HT2 antagonists and acetylcholinesterase (AChE) inhibitors were administered immediately after the training session. PCA- but not SCOP-induced amnesia was attenuated by the post-training administration of two benzomorphans, (+)N-allylnormetazocine and (±)pentazocine. Similarly, PCA-induced amnesia was reversed by the post-training administration of 5-HT2 antagonists, ritanserin and mianserin, but SCOP-induced amnesia was not. However, the AChE inhibitors, tetrahydroaminoacridine and physostigmine attenuated both PCA- and SCOP-induced amnesia when administered immediately after the training session. These results indicated that benzomorphans and 5-HT2 antagonists have antiamnestic effects in mice, as do AChE inhibitors. In addition, it is interesting that the patterns of ameliorating effect of benzomorphans were similar to those of 5-HT2 antagonists, which differ from those of AChE inhibitors.
IT 321-64-2
RL: BIOL (Biological study)
(amnesia to passive avoidance behavior response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



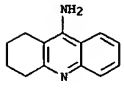
L11 ANSWER 122 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:644340 HCAPLUS
DOCUMENT NUMBER: 119:244340
TITLE: Three distinct domains in the cholinesterase molecule confer selectivity for acetyl- and butyrylcholinesterase inhibitors
AUTHOR(S): Radic, Zoran; Pickering, Natilie A.; Vellom, Daniel C.; Camp, Shelley; Taylor, Palmer
CORPORATE SOURCE: Dep. Pharmacol., Univ. California, San Diego, La Jolla, CA, 92093-0636, USA
SOURCE: Biochemistry (1993), 32(45), 12074-84
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB By examining inhibitor interactions with single and multiple site-specific mutants of mouse acetylcholinesterase, the authors have identified three distinct domains in the cholinesterase structure that are responsible for conferring selectivity for acetyl- and butyrylcholinesterase inhibitors. The first domain is the most obvious; it defines the constraints on the acyl pocket dimensions where the side chains of F295 and F297 primarily outline this region in acetylcholinesterase. Replacement of these phenylalanine side chains with the aliphatic residues found in butyrylcholinesterase allows for the catalysis of larger substrates and accommodates butyrylcholinesterase-selective alkyl phosphates such as isoOMPA. Also, elements of substrate activation characteristic of butyrylcholiesterases are evident in the F297I mutant. Substitution of tyrosines for F295 and F297 further alters the catalytic consts. The second domain is found near the lip of the active center gorge defined by two tyrosines, Y72 and Y124, and by W286; this region appears to be critical for the selectivity of bisquaternary inhibitors, such as BW284C51. The third domain defines the site of choline binding. Herein, in addition to conserved E202 and W86, a critical tyrosine, Y337, found only in the acetylcholinesterases is responsible for sterically occluding the binding site for substituted tricyclic inhibitors such as ethoproprazine. Anal. of a series of substituted acridines and phenothiazines defines the groups on the ligand and amino acid side chains in the site governing binding selectivity. Each of the three domains is defined by a cluster of aromatic residues. The two domains stabilizing the quaternary ammonium moieties also contain a neg. charge, which contributes to the stabilization energy of the resp. complexes.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholinesterase wild-type and mutant forms inhibition by, enzyme domains and determination of inhibitor selectivity in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



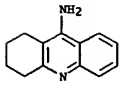
L11 ANSWER 123 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:643506 HCAPLUS
DOCUMENT NUMBER: 119:243506
TITLE: Combinations of parasympathomimetic agents with muscarinic antagonists for treating nicotine craving in smoking cessation
INVENTOR(S): Callaway, Enoch
PATENT ASSIGNEE(S): Univ. of California, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9318768	A1	19930930	WO 1993-US2650	19930311
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 630243	A1	19941228	EP 1993-908484	19930311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07505367	T2	19950615	JP 1993-516788	19930311
PRIORITY APPLN. INFO.:			US 1992-851914 A	19920316
			WO 1993-US2650 W	19930311

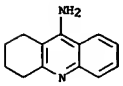
AB Craving in a nicotine-habituated patient is treated with a composition containing a nonspecific cholinergic agonist (e.g. a water-soluble physostigmine derivative) and a muscarinic antagonist (e.g. a water-soluble scopolamine derivative). Thus, smokers administered tablets containing 0.6 mg scopolamine-HBr, 0.6 mg physostigmine sulfate, and 0.5 g ascorbic acid (antioxidant) experienced craving relief for ≥2 h.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(nicotine craving abatement with muscarinic antagonist and, in tobacco smoking cessation)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



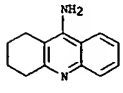
L11 ANSWER 124 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:617142 HCAPLUS
DOCUMENT NUMBER: 119:217142
TITLE: Tacrine (tetrahydroaminoacridine) and the metabolism of acetylcholine and choline
AUTHOR(S): Tucek, Stanislav; Dolezal, Vladimir
CORPORATE SOURCE: Inst. Physiol., Czech. Acad. Sci., Prague, 142 20, Czech Rep.
SOURCE: NATO ASI Series, Series H: Cell Biology (1993), (Phospholipids and Signal Transmission), 341-51
CODEN: NASBE4; ISSN: 1010-8793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several effects of tacrine on the metabolism of ACh(acetylcholine) and choline have been observed in cerebrocortical prisms prepared from Wistar white rats, independent of its cholinesterase-inhibiting activity. Tacrine increased the content and the synthesis of ACh in cortical prisms incubated at 3 mmol/L K+. The enhanced synthesis was associated with an enhanced utilization of choline from an intracellular source since the uptake of choline from the medium was inhibited. Tacrine had a pos. effect on the rate of ACh synthesis even in the presence of 10 μmpl/L HC-3. Tacrine increased the release of ACh from cortical prisms incubated at 3 mmol/L K+. Tacrine strongly diminished the release of ACh from the prisms evoked by depolarization with 50 mmol/L K+. It could be shown that the inhibition of the evoked ACh release was not a consequence of the inhibition of ACh synthesis. It seems possible that tacrine acted by blocking the voltage-sensitive CaZ+-channels. Tacrine inhibited the output of choline from cortical prisms into incubation media in expts. in which the prisms had been preincubated with a high concentration of choline, or in expts. in which the high-affinity uptake of choline had been blocked by HC-3. By restricting the efflux of choline from the cells, tacrine possibly increases the availability of intracellular choline for the synthesis of ACh, as observed in expts. with tissue incubation under resting conditions.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine and choline metabolism by cerebral cortex response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



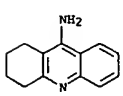
L11 ANSWER 125 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:598522 HCAPLUS
DOCUMENT NUMBER: 119:198522
TITLE: Three-dimensional structure of acetylcholinesterase and of its complexes with anticholinesterase drugs
AUTHOR(S): Sussman, J. L.; Harel, M.; Silman, I.
CORPORATE SOURCE: Dep. Struct. Biol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SOURCE: Chemico-Biological Interactions (1993), 87(1-3), 187-97
CODEN: CBINA8; ISSN: 0009-2797
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on the authors' recent x-ray crystallog. determination of the structure of acetylcholinesterase (AChE) from Torpedo california, it was possible for the 1st time to see, at atomic resolution, a protein binding pocket for the neurotransmitter, acetylchholine. It was found that the active site consists of a catalytic triad (S200-H440-E327) which lies close to the bottom of a deep and narrow gorge, which is lined with the rings of 14 aromatic amino acid residues. Despite the complexity of this array of aromatic rings, the authors suggested, on the basis of modeling which involved docking of the acetylcholine (ACh) mol. in an all-trans configuration, that the quaternary group of the choline moiety makes close contact with the indole ring of Trp-84. In order to study the interaction of AChE with anticholinesterase drugs at the structural level, the authors incorporated into the AChE crystals several different inhibitors, and have recently determined the 3-dimensional structure of AChE-edrophonium and AChE-tacrine complexes. The crystal structures of both of these complexes were in good agreement with the authors' model building of ACh bound in the active site of AChE and indicated the interactions of these 2 drugs with the enzyme.
IT 321-64-2D, Tacrine, acetylcholinesterase complexes
RL: PRP (Properties)
(crystal structure of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



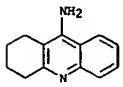
L11 ANSWER 126 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:595891 HCAPLUS
DOCUMENT NUMBER: 119:195891
TITLE: Cholinesterase inhibitor effects on extracellular acetylcholine in rat cortex
AUTHOR(S): Messamore, Erik; Warpman, Ulrika; Ogane, Nobuo; Giacobini, Ezio
CORPORATE SOURCE: Sch. Med., South. Illinois Univ., Springfield, IL, 62794-9230, USA
SOURCE: Neuropharmacology (1993), 32(8), 745-50
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A microdialysis technique was used to sample acetylcholine (ACh) from the cerebral cortex of conscious rats. The authors thus investigated the effects of systematically administered cholinesterase inhibitors (ChEI) such as physostigmine (300 μg/kg), heptylphysostigmine (5 mg/kg) and tetrahydroaminoacridine (tacrine, 5 mg/kg) on extracellular ACh levels. Baseline quantities of extracellular ACh could be detected, even in the absence of ChEI. ACh levels increased to 1100% over baseline within 30 min of physostigmine administration and returned to control levels after 1.25 h. Heptylphysostigmine elicited a maximal increase of 1000% within 1.5 h, and the effect persisted ≤9.5 h. A 500% increase was observed 1.5 h after tacrine administration, and ACh returned to control levels after 4 h. Although the ACh effects observed in this study correlated with previously determined levels of acetylcholinesterase (AChE) inhibition, the authors conclude that measures of cortical AChE activity alone are not sufficient to predict extracellular ACh levels following systemic ChEI administration.
IT 321-64-2, Tacrine
RL: PROC (Process)
(acetylcholine of brain after administration of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



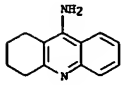
L11 ANSWER 127 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:595889 HCAPLUS
DOCUMENT NUMBER: 119:195889
TITLE: Pharmacological characterization of acetylcholine-stimulated [35S]-GTPγS binding mediated by human muscarinic m1-m4 receptors: Antagonist studies
AUTHOR(S): Lazareno, S.; Birdsall, N. J. M.
CORPORATE SOURCE: MRC Collab. Cent., London, NW7 1AD, UK
SOURCE: British Journal of Pharmacology (1993), 109(4), 1120-7
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have used dose-ratio anal. to estimate functionally the affinity consts. (pKb) and Schild slope factors of a range of selective or atypical antagonists at human muscarinic m1-m4 receptors. The functional response was the stimulation by acetylcholine of [35S]GTPγS binding to membranes from Chinese hamster ovary (CHO) cells stably expressing individual receptor subtypes. A novel exptl. design and anal. was used which allowed the estimation of affinity and Schild slope factor from a single antagonist inhibition curve, and the results were compared with other methods of anal., both theor. valid and invalid. In general, the affinity ests. were very similar to previously reported values obtained in binding studies with animal tissues and cloned human receptors and the Schild slope factors were close to unity. The results demonstrate the validity of the assay and provide no evidence for species differences in antagonist affinity for muscarinic receptor subtypes. The results confirm both the utility of himbacine in distinguishing between m1 and m4 receptors and a previously reported modest m4-selectivity for tropicamide and secoverine. The cholinesterase inhibitor, tacrine, had a potency profile similar to that of gallamine but with less selectivity. Its affinity could not be determined since it had Schild slope factors of about 2 at all subtypes. O-Methoxysilahexocyclium had only a modest selectivity for the m1 subtype.
IT 321-64-2, Tacrine
RL: PROC (Process)
(muscarinic receptor binding of, in receptor subtype characterization)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



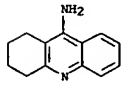
L11 ANSWER 128 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:574115 HCAPLUS
DOCUMENT NUMBER: 119:174115
TITLE: Effects of muscarinic receptor agonists and anticholinesterase drugs on high voltage spindles and slow waves
AUTHOR(S): Riekkinen, Paavo, Jr.; Riekkinen, Minna; Fisher, A.; Ekonsalo, Tommi; Sirvio, Jouni
CORPORATE SOURCE: Dep. Neurol., Univ. Kuopio, Kuopio, SF-70211, Finland
SOURCE: European Journal of Pharmacology (1993), 240(1), 1-7
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of muscarinic agonists (AF102B, pilocarpine, oxotremorine) and anticholinesterases (physostigmine, tetrahydroaminoacridine) were investigated on the incidence of thalamically generated rhythmic high voltage spindles and on scopolamine (0.2 mg/kg)-induced neocortical slow wave activity (i.e. increased sum amplitude value of the 1-20 Hz band in a quant. electroencephalog. (qEEG) anal. in rats). AF102B and pilocarpine decreased high voltage spindles and scopolamine increased sum amplitude values at 3 and 9 mg/kg, but not at 1 mg/kg. Oxotremorine was less potent than AF102B or pilocarpine in suppressing high voltage spindles. Oxotremorine had no effect on the scopolamine-induced qEEG changes. Tetrahydroaminoacridine decreased high voltage spindles at 1, 3 and 9 mg/kg and slow waves at 9 mg/kg. Physostigmine decreased high voltage spindles and slow waves at 0.12 and 0.36 mg/kg. Based on the present results the authors propose that agonists possessing muscarinic M1 receptor activity are effective in decreasing high voltage spindles and scopolamine-induced slow wave activity, but agonists showing predominant muscarinic M2 receptor activity may be less effective in decreasing high voltage spindles and slow waves. Furthermore, tetrahydroaminoacridine decreased high voltage spindles at doses lower than those required to decrease scopolamine-induced slow waves. Physostigmine decreased high voltage spindles and slow waves over the same dose range. This result may indicate that non-cholinergic mechanisms are involved in the tetrahydroaminoacridine-induced decrease in high voltage spindles.
IT 321-64-2
RL: BIOL (Biological study)
(brain high voltage spindles and slow waves response to, anticholinesterase activity in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 129 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:574092 HCAPLUS
DOCUMENT NUMBER: 119:174092
TITLE: Chronic treatments with cholinoceptor drugs influence spatial learning in rats
AUTHOR(S): Abdulla, F. A.; Calaminici, M. R.; Stephenson, J. D.; Sinden, J. D.
CORPORATE SOURCE: Dep. Psychol., Inst. Psychiatry, London, SE5 8AF, UK
SOURCE: Psychopharmacology (Berlin, Germany) (1993), 111(4), 508-11
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nicotine, scopolamine, oxotremorine, diisopropyl-fluorophosphate (DFP) and tetrahydroaminoacridine (THA) were administered chronically to different groups of rats in doses reported to alter central muscarinic and/or nicotinic receptor nos. Beginning 24 h after final drug injection, the groups were compared to a vehicle control group on acquisition of a hidden platform position in the Morris water maze over 20 trials with a 30-min inter-trial interval. Chronic treatment with either nicotine or scopolamine significantly improved the rate of learning, but oxotremorine and DFP retarded learning and THA had no effect on learning. The chronic drug effects on behavior were consistent with known effects of the injected drugs on muscarinic and nicotinic binding in the forebrain and on the sensitivity of frontal cortex neurons to iontophoretically applied cholinoceptor agonists. However, alternative explanations for the observed changes cannot be ruled out, since the drugs used are known to have a wide range of effects on other neurotransmitters.
IT 321-64-2
RL: BIOL (Biological study)
(spatial learning response to chronic administration of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



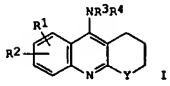
L11 ANSWER 130 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:574051 HCAPLUS
DOCUMENT NUMBER: 119:174051
TITLE: Interaction of tacrine at M1 and M2 cholinoceptors in guinea pig brain
AUTHOR(S): Szilagyi, Maria; Lau, Wai Man
CORPORATE SOURCE: Mater. Res. Lab., Def. Sci. Technol. Organ., Ascot Vale, 3032, Australia
SOURCE: Pharmacology (1993), 47(4), 223-9
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine (THA) selectively modulates binding of M1 ligands in an allosteric fashion causing pos. cooperativity. The binding affinity of THA to M1 and M2 cholinoceptors is similar. It is therefore proposed that the allosteric selectivity of THA is a function of the binding site and not of THA itself. Its interaction of M1 and M2 cholinoceptors was examined in guinea pig brain homogenates using the selective M1 and M2 antagonists [3H]-pirenzepine ([3H]PZ) and [3H]AF-DX 384. The dissociation consts. were 0.36 nmol/L for the M1 receptor and 0.23 nmol/L for the M2 receptor. The authors also compared the binding of THA and methoctramine (MTA) at M2 receptors. Tacrine displayed similar binding affinity for both M1 and M2 receptor subtypes. MTA was 100 times more potent an inhibitor of [3H]AF-DX 384 binding at M2 receptors than THA. In addition, THA was found to slow the dissociation of [3H]PZ from the M1 receptor. In contrast, the dissociation of [3H]AF-DX 384 from M2 receptor subtypes was unaffected. The authors conclude that THA acts as an agonist at M1 cholinoceptors because it slowed the dissociation of [3H]PZ. At M2 cholinoceptors its nature is that of an antagonist because it had no effect on [3H]AF-DX 384 dissociation
IT 321-64-2, Tacrine
RL: PRP (Properties)
(interaction of, with M1 and M2 cholinoceptors in brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



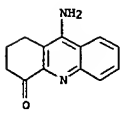
L11 ANSWER 131 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:539138 HCAPLUS
DOCUMENT NUMBER: 119:139138
TITLE: Preparation of aminoacridines for treatment of senile dementia
INVENTOR(S): Fukumi, Hiroshi; Sakamoto, Toshiaki; Iwata, Nobuyoshi; Matsui, Yoshiki
PATENT ASSIGNEE(S): Sankyo Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05059010	A2	19930309	JP 1991-223837	19910904
PRIORITY APPLN. INFO.:			JP 1991-223837	19910904

OTHER SOURCE(S): MARPAT 119:139138
GI

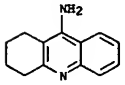


AB Aminoacridines I (R1, R2 = H, C1-4 alkyl or alkoxy, halo; R3, R4 = H, C1-4 or C7-13 alkyl, C6-10 aryl, acyl; Y = CO, HOCH; R3 = R4 ≠ acyl) and their pharmacol. acceptable salts, which inhibit acetylcholine esterase, are prepared Treatment of 5-chloro-2-(6-oxo-1-cyclohexen-1-yl)aminobenzonitrile with Li diisopropylamide in THF at room temperature for 2 h gave 25% 9-amino-7-chloro-1,2-dihydroacridin-4(3H)-one, which was treated with NaBH4 in MeOH at room temperature for 30 min to afford 25% 9-amino-7-chloro-1,2,3,4-tetrahydroacridin-4-ol. The product strongly inhibited acetylcholine esterase (no further information).
IT 122910-29-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of)
RN 122910-29-6 HCAPLUS
CN 4(1H)-Acridinone, 9-amino-2,3-dihydro- (9CI) (CA INDEX NAME)

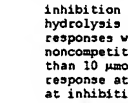


L11 ANSWER 131 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

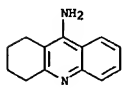
L11 ANSWER 132 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:531409 HCAPLUS
DOCUMENT NUMBER: 119:131409
TITLE: The effects of tacrine and zacopride on the performance of adult rats in the working memory task
AUTHOR(S): Jakala, Pekka; Sirvio, Jouni; Riekkinen, Paavo J.
CORPORATE SOURCE: Dep. Neurol., Univ. Kuopio, Kuopio, Finland
SOURCE: General Pharmacology (1993), 24(3), 675-9
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study investigated the effects of tacrine (an inhibitor of acetylcholinesterase) and zacopride (the antagonist of 5-HT3 receptors) on the performance of adult rats in a continuous operant delayed non-matching to position task assessing spatial working memory. Adult rats had a decline in the percent correction responses at the longest delays (16 and 30 s) in this task. Tacrine (1.0 mg/kg) or zacopride (0.0025, 0.05, 1.0 mg/kg) did not increase the percent correct responses at any time delays. The higher dose of tacrine reduced behavioral activity (e.g. the decreased number of trials completed and increased sample press latency) of rats during memory testing, and it slightly increased choice accuracy across all the delays. The combination of zacopride (1.0 mg/kg) and tacrine (1.0 mg/kg) increased the percent correct responses at the shortest delays, but not at the longest delays. These results indicate a non-mnemonic improvement in the accuracy performance of rats, and they suggest that the effects of acute, systemic administrations of zacopride (which is thought to increase the release of acetylcholine) or/and tacrine (which inhibits the breakdown of acetylcholine) do not improve spatial working/short-term memory in rats.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(spatial and short-term memory response to, cholinergic system stimulation in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 133 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:462970 HCAPLUS
DOCUMENT NUMBER: 119:62970
TITLE: Effects of Tacrine on brain muscarinic -receptor-mediated second-messenger signals
AUTHOR(S): Kiefer-Day, Jennifer S.; Abdallah, El Sayed A. M.; Forray, Carlos; Lee, Norman H.; Kim, Ok Nyu; El-Fakahany, Esam E.
CORPORATE SOURCE: Med. Sch., Univ. Minnesota, Minneapolis, MN, 55455, USA
SOURCE: Pharmacology (1993), 47(2), 98-110
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to investigate the effects of 9-amino-1,2,3,4-tetrahydroacridine (THA; Tacrine) on muscarinic -receptor-linked second-messenger systems in rat brain and to determine the selectivity and mechanisms of these effects. Both competitive and noncompetitive antagonism was revealed in saturation radioligand binding studies performed in cortical and striatal tissue, depending on THA concentration
Micromolar THA concns. blocked muscarinic-receptor-mediated inhibition of cAMP formation and stimulation of phosphoinositide (PI) hydrolysis with poor selectivity between the two responses. While both responses were blocked in the same concentration range (4-60 μmol/L), noncompetitive antagonism of PI hydrolysis occurred at THA concns. greater than 10 μmol/L while competitive antagonism was displayed for the cAMP response at concns. of THA up to 40 μmol/L. THA was equally effective at inhibiting PI hydrolysis stimulated by histamine, phenylephrine or oxotremorine-M, when these agonists were employed in concns. equal to their EC50s for the response. THA did not antagonize PI hydrolysis mediated by the quisqualate receptor at any agonist concentration used. Furthermore, THA blocked carbachol- but not morphine-induced inhibition of forskolin-stimulated cAMP formation in the striatum.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(muscarinic antagonism by, in brain, second messenger signal modulation in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

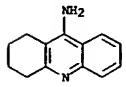


L11 ANSWER 134 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:462944 HCAPLUS
DOCUMENT NUMBER: 119:62944
TITLE: Effect of in vivo microdialysis of 1,2,3,4-tetrahydro-9-aminoacridine (THA) on the extracellular concentration of acetylcholine in the striatum of anesthetized rats
AUTHOR(S): Xiao, Wenbin; Nordberg, Agneta; Zhang, Xiao
CORPORATE SOURCE: Biomed. Cent., Uppsala Univ., Uppsala, Swed.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 265(2), 759-64
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB THA (tacrine) is a potent cholinesterase (ChE) inhibitor which is under consideration for the treatment of Alzheimer's disease. This paper examines the effect of in vivo microdialysis of THA, THB-013 (an analog of THA) and physostigmine on the extracellular concentration of acetylcholine (ACh) in the striatum of anesthetized rats, as well as their effects on in vitro striatal ChE activity. In addition, the interaction of THA and physostigmine with cholinergic receptors in rat striatum has been investigated. All three drugs inhibited ChE activity and increased the extracellular concentration of ACh in a concentration-dependent manner. In the presence of THA, atropine induced a smaller increase in extracellular ACh concns. than it did in the presence of physostigmine, under exptl. conditions in which THA (100 μM) and physostigmine (10 μM) produced an equivalent effect on ChE activity. THA bound significantly to both muscarinic and nicotinic receptors in rat striatum, whereas physostigmine did not show significant binding. THA (100 μM) and physostigmine (10 μM) produced an additive effect on the extracellular concentration of ACh, and the addition of THA (10 μM) to physostigmine (1 μM) produced further inhibition of in vitro ChE activity. 4-Aminopyridine (100 μM), a K+ channel blocker, showed no detectable effect by itself on the extracellular concentration of ACh, however, it significantly increased the extracellular concentration of ACh in the presence of physostigmine (10 μM). The increase in ACh concns. evoked by K+ was significantly lower in the presence of THA (100 μM) than in the presence of physostigmine (10 μM), and also significantly lower in the presence of physostigmine (10 μM) plus 4-aminopyridine (100 μM) than in the presence of physostigmine (10 μM) plus THA (100 μM). These results indicate that multiple mechanisms are possibly involved in the THA regulation of extracellular ACh concns. in the striatum of anesthetized rats.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(regulation of acetylcholine by, in striatum, Alzheimer's treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

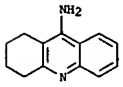


L11 ANSWER 134 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 135 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:440816 HCAPLUS
DOCUMENT NUMBER: 119:40816
TITLE: Effects of some cholinergic agonists on neocortical slow wave activity in rats with basal forebrain lesions
AUTHOR(S): Vanderwolf, C. H.; Raithby, Angela; Snider, Melissa; Cristi, Carolina; Tanner, Carolyn
CORPORATE SOURCE: Dep. Psychol., Univ. West. Ontario, London, ON, N6A 5C2, Can.
SOURCE: Brain Research Bulletin (1993), 31(5), 515-21
CODEN: BRBUDU; ISSN: 0361-9230
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chronic rats, prepared with unilateral injections of kainic acid in the left basal forebrain, displayed prominent large amplitude slow wave activity in the neocortex ipsilateral to the injection. Oxotremorine and pilocarpine, given systemically following pretreatment with Me scopolamine to block peripheral muscarinic effects, restored low voltage fast activity (LVFA) in a dose-related manner. Oxotremorine was more potent than pilocarpine. Arecoline was not consistently active. Tetrahydroaminoacridine abolished abnormal 4-6 Hz rhythmical slow waves in the left neocortex but had little effect on large amplitude irregular slow waves. Direct-acting cholinergic agonists can restore near-normal neocoritical activity after extensive cholinergic deafferentation of the neocortex.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(brain basal forebrain cholinergic lesions from kainic acid response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

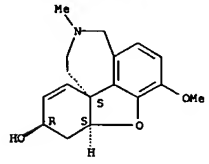


L11 ANSWER 136 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:401462 HCAPLUS
DOCUMENT NUMBER: 119:1462
TITLE: Autoradiographic demonstration of an increase in muscarinic cholinergic receptors in cerebellar granule cells treated with tetrahydroaminoacridine
AUTHOR(S): Sunaga, Katsuyoshi; Chuang, De Maw; Ishitani, Ryoichi
CORPORATE SOURCE: Group Neuropharmacol., Josai Univ., Sakado, 350-02, Japan
SOURCE: Neuroscience Letters (1993), 151(1), 45-7
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The neurotropic and neurosurviving effects of 9-amino-1,2,3,4-tetrahydroacridine (THA), a putative antidementia agent, were studied in cultured granule cells using biochem. and morphol. methods. The addition of 30 μM THA to cultures grown in 15 mM K+-containing media markedly increased cell survival and enhanced [3H]N-methylscopolamine binding to muscarinic cholinergic receptors (mAChRs). Furthermore, receptor autoradiog. studies revealed that neuronal cells were labeled over both cell bodies and fibers by the [3H]receptor ligand. These observations provide direct evidence that THA promotes the expression of mAChR binding sites in differentiating cerebellar granule cells.
IT 321-64-2
RL: BIOL (Biological study)
(muscarinic receptors in cerebellum granule cells increase by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

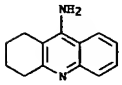


L11 ANSWER 137 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:400160 HCAPLUS
DOCUMENT NUMBER: 119:160
TITLE: Indirect detection of anti-acetylcholinesterase compounds in microcolumn liquid chromatography using packed bed reactor with immobilized human red blood cell acetylcholinesterase and choline oxidase
AUTHOR(S): Salamoun, Jaroslav; Remien, Jorg
CORPORATE SOURCE: Walther-Straub Inst. Pharmacol. Toxicol., Munich, 8000/2, Germany
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1992), 10(10-12), 931-6
CODEN: JPBADA; ISSN: 0731-7085
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The inhibiting compds. were separated by micro-column liquid chromatog. in the mobile phase containing the natural substrate acetylcholine. A home-made packed bed microbioreactor system containing immobilized enzyme acetylcholinesterase (AChE) in human red blood cell membrane and choline oxidase (ChO) from alcaligenes was used for the post-column conversion of acetylcholine to hydrogen peroxide which was detected by an electrochem. detector. The inhibition effect of the solutes caused a decrease in the acetylcholinesterase activity, a decrease in the formation of hydrogen peroxide and also a decrease in the response corresponding to the concentration of the solutes. The rate of the enzyme regeneration was also recorded. The micro-system was compared with a conventional LC system comprising com. prepared enzyme reactor. The stability of the enzymes is at least 3 wk at ambient temperature The limit of detection depends on biol. activity of inhibition and for galanthamine was 1 pmol.
IT 357-70-0, Galanthamine
RL: ANT (Analyte); ANST (Analytical study)
(detection of, as acetycholinesterase inhibitor, by microcolumn liquid chromatog, human enzyme immobilization in)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

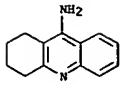


L11 ANSWER 138 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:229111 HCAPLUS
DOCUMENT NUMBER: 118:229111
TITLE: 3-D structure of acetylcholinesterase and complexes of it with anticholinesterase agents
AUTHOR(S): Sussman, J. L.; Harel, M.; Silman, I.
CORPORATE SOURCE: Dep. Struct. Biol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SOURCE: Jerusalem Symposia on Quantum Chemistry and Biochemistry (1992), 25(Membrane Proteins: Structures, Interactions and Models), 161-75
CODEN: JSQCA7; ISSN: 0075-3696
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In order to study the interactions of acetylcholinesterase (AChE) with anticholinesterase agents, in detail, a series of different inhibitors were soaked into crystals of AChE and 3-D structure of AChE:edrophonium and AChE:tacrine were determined The crystal structures of both of these complexes are in good agreement with the model of acetylcholine bound in the active site of AChE and indicate the interactions of these two drugs with the enzyme.
IT 321-64-2D, Tacrine, acetylcholinesterase complexes
RL: PRP (Properties)
(structure of, crystallog. study of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

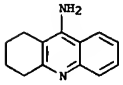


L11 ANSWER 139 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:225499 HCAPLUS
DOCUMENT NUMBER: 118:225499
TITLE: Long-term biphasic effects of lithium treatment on phospholipase C-coupled M3-muscarinic acetylcholine receptors in cultured cerebellar granule cells
AUTHOR(S): Gao, Xiao Ming; Fukamauchi, Fumihiko; Chuang, De Maw
CORPORATE SOURCE: Biol. Psychiatry Branch, Natl. Ment. Health, Bethesda, MD, 20892, USA
SOURCE: Neurochemistry International (1993), 22(4), 395-403
CODEN: NEUIDS; ISSN: 0197-0186
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have studied the long-term effects of lithium on neuronal morphol. and the functional expression of phospholipase C-coupled m3-muscarinic acetylcholine receptors (mAChRs) in cerebellar granule cells. There was a biphasic dose-dependent effect on cell morphol. following treatment with lithium for 7 days. At low concns. (≤2 mM), this drug elicited an increase in the number and thickness of connecting nerve fibers, and the size of neuronal aggregates. At high concns. (5-10 mM), lithium induced a severe deterioration of cell morphol., which ultimately resulted in neuronal death. Carbachol-induced phosphoinositide (PI) turnover was similarly affected by lithium treatment with a significant potentiation at concns. up to 2 mM and a marked inhibition at doses higher than 5 mM due to lithium-induced neurotoxicity. The biphasic effect on mAChR-mediated PI hydrolysis was associated with corresponding changes in the maximal extent of carbachol-induced inositol phosphate accumulation, and was accompanied by similar changes in [3H]N-methyl-scopolamine binding to mAChRs and the levels of mRNAs for m3-mAChR and c-Fos. The up-regulation of m3-mAChR mRNA induced by low concns. of lithium was associated with a down-regulation of m2-mAChR mRNA and no change in either total RNA or β-actin mRNA. Lithium's effects on m2- and m3-mAChR mRNAs were time-dependent, requiring a pretreatment time of ≥3 days. The biphasic effect was also demonstrated by the binding of [3H]ouabain to Na+, K+-ATPase, which was shown to be a convenient method for quantifying viable neurons. The neurotoxic effect induced by treatment with high concns. of lithium was not prevented by known neuroprotective/neurotrophic substances such as 9-amino-tetrahydroacridine or N-methyl-D-aspartate, or the co-presence of excess myo-inositol. Since the neurotrophic influences was induced by concns. of lithium which overlap the clin. dose range and require long-term treatment, this effect might be relevant to the efficacy of this drug in the treatment of manic-depressive illness.
IT 321-64-2
RL: BIOL (Biological study)
(neurotoxicity from lithium response to, in cerebellar granular cells)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

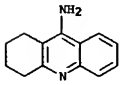
L11 ANSWER 139 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 140 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:205130 HCAPLUS
DOCUMENT NUMBER: 118:205130
TITLE: Discriminative stimulus properties of NIK-247 and tetrahydroaminoacridine, centrally active cholinesterase inhibitors, in rats
AUTHOR(S): Yamamoto, Tsuneyuki; Ohno, Masuo; Sugimachi, Keiko; Ueki, Showa
CORPORATE SOURCE: Fac. Pharm. Sci., Kyushu Univ., Fukuoka, 812, Japan
SOURCE: Pharmacology, Biochemistry and Behavior (1993), 44(4), 769-75
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The discriminative stimulus effect of the novel centrally active cholinesterase inhibitor, NIK-247, was investigated in rats and compared with that of tetrahydroaminoacridine (THA). Rats were trained to discriminate either 10 mg/kg NIK-247 or 1.0 mg/kg THA from saline in a two-lever food-reinforced procedure. The stimulus effect of NIK-247 was substituted for by the cholinesterase inhibitors, THA and physostigmine. The THA stimulus was substituted for by NIK-247 and physostigmine. The muscarinic receptor agonist arecoline substituted for the NIK-247 and THA stimuli. Both stimulus effects of NIK-247 and THA were blocked by the muscarinic antagonist scopolamine. The dopaminergic-activating drugs amantadine and lisuride substituted for the stimulus effects of NIK-247 and THA. However, neither the NIK-247 nor the THA stimulus was antagonized by the dopamine antagonists haloperidol, SCH 23390, and sulpiride. These results suggest that the discriminative stimulus effects of NIK-247 and THA are mediated by muscarinic receptors, and that the dopaminergic activity resulting from cholinergic activation may account for some part of both stimuli.
IT 321-64-2
RL: BIOL (Biological study)
(discriminative stimulus properties of, as centrally active cholinesterase inhibitor)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

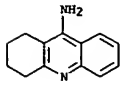


L11 ANSWER 141 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:94257 HCAPLUS
DOCUMENT NUMBER: 118:94257
TITLE: Tetrahydroaminoacridine is neurotrophic and promotes the expression of muscarinic receptor-coupled phosphoinositide turnover in differentiating cerebellar granule cells
AUTHOR(S): Sunaga, Katsuyoshi; Chuang, De Maw; Ishitani, Ryoichi
CORPORATE SOURCE: Group Neuropharmacol., Josai Univ., Sakado, 350-02, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1993), 264(1), 463-8
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have investigated whether 9-amino-1,2,3,4-tetrahydroacridine (THA), a drug with potential antidementia activity, has a trophic action on differentiating cerebellar granule cells by using the method of [3H]inositol incorporation into inositol-containing phospholipid. Addition of THA (30-50 μM) prevented the extensive neuronal degeneration which occurred in the growth medium containing "low" K+ (15 mM). These effects were similar to the neuroprotective action caused by the presence of 100 μM N-methyl-D-aspartate (NMDA). Neurotrophic effects of THA and NMDA on cells grown in low K+ were also demonstrated by direct microscopic examination of cellular morphol. Measurement of phosphoinositide (PI) response in the rescued cells indicated that NMDA modestly promoted the PI response to carbachol and norepinephrine but markedly stimulated the activity induced by glutamate. In contrast, although THA had little or no influence on the maturation of the norepinephrine- and glutamate-induced PI response, it selectively enhanced the activity stimulated by carbachol. Furthermore, the THA treatment drastically increased the Vmax value of carbachol-induced PI turnover with no significant alteration in the EC50 value. Scatchard anal. of the binding of N-[3H]methylscopolamine to intact granule cells indicated a selective increase in the maximum binding value in cells grown in THA-supplementing medium. These observations suggest that THA seems to selectively up-regulate muscarinic cholinergic receptors.
IT 321-64-2
RL: PRP (Properties)
(neurotrophic effect of, on differentiating cerebellar granule cells, muscarinic receptor up-regulation in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

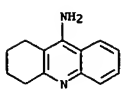


L11 ANSWER 141 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

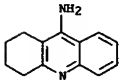
L11 ANSWER 142 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:32818 HCAPLUS
DOCUMENT NUMBER: 118:32818
TITLE: Two allosteric modulators interact at a common site on cardiac muscarinic receptors
AUTHOR(S): Ellis, John; Seidenberg, Margaret
CORPORATE SOURCE: Dep. Psychiatry, Univ. Vermont, Burlington, VT, 05405, USA
SOURCE: Molecular Pharmacology (1992), 42(4), 638-41
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The abilities of gallamine, obidoxime, tetrahydroaminoacridine (THA), and 8-(N,N-diethylamino)octyl-3,4,5-trimethoxybenzoate (TMB-8) to alter the rate of dissociation of N-[3H]methylscopolamine from rat cardiac muscarinic receptors were investigated. All four ligands monotonically slowed the dissociation, with the order of potency gallamine > TMB-8 > THA > obidoxime. There was a dramatic different in the efficacy of these allosteric modulators. Gallamine, TMB-8, and THA slowed the dissociation of N-methylscopolamine by >90% at maximally effective concns., whereas obidoxime was capable of slowing it by only about 50%. In a manner analogous to the action of a partial agonist, obidoxime was able to partially reverse the effects of the other three modulators. Furthermore, the concentration-dependent effects of combinations of obidoxime and gallamine were in good agreement with the model of competitive interaction between these two ligands. These results provide the first evidence that two muscarinic allosteric modulators interact competitively at a well defined site.
IT 321-64-2
RL: BIOL (Biological study)
(methylscopolamine association from heart muscarinic receptors response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 143 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:16181 HCAPLUS
DOCUMENT NUMBER: 118:16181
TITLE: Investigation of the mechanism of the effect of tacrine (tetrahydroaminoacridine) on the metabolism of acetylcholine and choline in brain cortical prisms
AUTHOR(S): Dolezal, V.; Rucek, S.
CORPORATE SOURCE: Inst. Physiol., Czech. Acad. Sci., Prague, Czech.
SOURCE: Journal of Neural Transmission: Parkinson's Disease and Dementia Section (1992), 4(4), 303-18
CODEN: JNPSEJ; ISSN: 0936-3076
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism by which tacrine increases the content and synthesis of acetylcholine (ACh) in cerebrocortical prisms exposed to an irreversible inhibitor of cholinesterases and incubated under resting conditions (Dolezal and Tucek, 1991) is not known. As found in the present expts., this effect of tacrine is only apparent if its application had been preceded by a period of preincubation, but the preincubation is ineffective if it occurs in the presence of hemicholinium-3. Apparently, choline or a choline-containing compound accumulates in the slices during the preincubation and is then utilized for the enhanced synthesis of ACh in the presence of tacrine. Tacrine did not induce a decrease in the amount of radiolabel that had been incorporated from choline into acid-insol. compds., which suggests that the choline which is used for the synthesis of addnl. ACh does not originate from choline lipids. However, tacrine was found to diminish the efflux of choline from prisms which had been preincubated with an increased concentration of choline in the medium, and from prisms incubated in the presence of hemicholinium-3. It also diminished the efflux of radioactive choline that had accumulated in the prisms during preincubation with a very low concentration of tacrine, when the prisms were subsequently incubated with 4-aminopyridine. It is proposed that the potency of tacrine to increase the content and synthesis of ACh in cerebrocortical prisms whose cholinesterases had been inhibited is due to its ability to diminish the efflux of endogenous choline from the nerve terminals.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine and choline metabolism in brain cortex response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

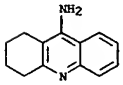


L11 ANSWER 144 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:605134 HCAPLUS
DOCUMENT NUMBER: 117:205134
TITLE: Metrifonate and tacrine: a comparative study of their effect on acetylcholine dynamics in mouse brain
AUTHOR(S): Nordgren, I.; Karlen, B.; Kinland, M.
CORPORATE SOURCE: Dep. Toxicol., Karolinska Inst., Stockholm, S-104 01, Swed.
SOURCE: Pharmacology & Toxicology (Oxford, United Kingdom) (1992), 71(3, Pt. 1), 236-40
CODEN: PHTOEH; ISSN: 0901-9928
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine (THA, tacrine) and metrifonate are cholinesterase inhibitors used in the treatment of Alzheimer disease. In exptl. animals they inhibit acetylcholinesterase activity and increase brain acetylcholine levels. Their effects at 2 dose levels on the dynamics of acetylcholine in the mouse brain were studied. Metrifonate at 10 and 30 mg/kg i.p., doses known to cause cholinesterase inhibition, had no effect on the levels of acetylcholine or choline or on the rate of synthesis of acetylcholine. THA (3 mg/kg i.p.) had no effect on the levels of acetylcholine and choline but had a short-lasting decreasing effect on the synthesis rate of acetylcholine. THA (10 mg/kg i.p.) increased the levels of acetylcholine and choline and markedly decreased the synthesis rate of acetylcholine. At this dose, the animals showed severe cholinergic effects, e.g. tremor and salivation. A moderate cholinesterase inhibition in the brain may facilitate the cholinergic nerve transmission. The inhibition is obtained at a broader dose range of metrifonate than of THA.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(brain acetylcholine metabolism responses to, Alzheimer disease treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

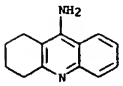


L11 ANSWER 145 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:563823 HCAPLUS
DOCUMENT NUMBER: 117:163823
TITLE: Prejunctional actions of tacrine on autonomic neuroeffector transmission in rabbit isolated pulmonary artery and rat isolated atria
AUTHOR(S): Fabiani, Maurizio E.; Kabo, Peter; Story, David F.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Melbourne, Parkville, Australia
SOURCE: Clinical and Experimental Pharmacology and Physiology (1992), 19(9), 631-43
CODEN: CEXPB9; ISSN: 0305-1870
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study investigated the effects of tacrine (1,2,3,4-tetrahydro-9-aminoacridine) on the resting and stimulation-induced (SI) release of radioactive substances from isolated prepns. of rat atria and rabbit pulmonary artery in which the noradrenergic transmitter stores had been labeled with [3H]noradrenaline, and from rat atrial prepns. in which cholinergic transmitter stores had been labeled with [3H] acetylcholine. In addition, the effect of tacrine on the uptake of [3H]noradrenaline by noradrenergic nerves in rat atria was determined
Tacrine
produced concentration-dependent increases in the resting efflux of radioactivity
from both the [3H]noradrenaline-loaded artery and atrial prepns. Blockade of neuronal amine transport with desipramine reduced the release of radioactivity evoked by tacrine from atria but not that evoked from artery prepns. Inhibition of monoamine oxidase by pargyline pretreatment markedly reduced the tacrine-evoked release of radioactivity in both atrial and artery prepns. The radioactivity released from [3H]noradrenaline-labeled rat atrial prepns. by 30 μmol/L tacrine consisted entirely of the deaminated metabolite [3H]DOPEG. The evoked release of [3H]DOPEG from atria was reduced by approx. 50% by desipramine (1 μmol/L). When atrial monoamine oxidase had been inhibited by pargyline treatment in vivo and in vitro, 30 μmol/L tacrine evoked the release of [3H]noradrenaline instead of [3H]DOPEG. However, the amts. of [3H]noradrenaline released by tacrine when monoamine oxidase was inhibited were only about 25% of the amts. of [3H]DOPEG released in untreated atria. Tacrine, in concns. of 1 and 10 μmol/L, enhanced the release of radioactivity evoked by field stimulation of [3H]noradrenaline-loaded rabbit pulmonary artery prepns. This effect was unaltered by desipramine or pretreatment with pargyline. However, in artery prepns. pretreated with pargyline, a high concentration of tacrine (100 μmol/L) markedly reduced
SI efflux. In contrast to the findings with artery prepns., tacrine (1-30 μmol/L) did not alter SI efflux in rat atrial prepns. It is concluded that tacrine displaces noradrenaline from intraneuronal transmitter stores of sympathetically-innervated tissues, and that the displaced amine is totally metabolized by monoamine oxidase before leaving the nerve terminals. When deamination of neuronal cytoplasmic noradrenaline is prevented, only a portion of the noradrenaline displaced from storage vesicles passes to the extracellular space. It is likely that the transfer of cytoplasmic noradrenaline out of the terminals is limited by the activity of the amine transport mechanism. Tacrine, in concns. of 30 and 100 μmol/L, reduced the uptake radioactivity by rat atria incubated for-5 min periods in [3H]noradrenaline to approx. 83 and 26%, resp., of control uptake. Desipramine was much more potent than tacrine in

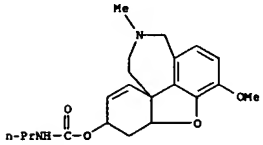
L11 ANSWER 145 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
inhibiting [3H]noradrenaline uptake: 1 μmol/L desipramine reduced the uptake radioactivity to approx. 18% of the control. Tacrine (30 μmol/L) did not alter the resting efflux of radioactivity from [3H] acetylcholine-labeled rat atrial prepns., but it reduced the efflux of radioactivity evoked by stimulation of intramural cholinergic nerves. The inhibition of SI efflux in the [3H]acetylcholine -labeled atria may have been mediated by acetylcholine that had accumulated as a consequence of the anticholinesterase activity of tacrine at cholinergic nerve terminals.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(cholinergic and noradrenergic transmitter release response to, in pulmonary artery and atria)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



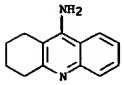
L11 ANSWER 146 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:400744 HCAPLUS
DOCUMENT NUMBER: 117:744
TITLE: Effects of four non-cholinergic cognitive enhancers in comparison with tacrine and galanthamine on scopolamine-induced amnesia in rats
AUTHOR(S): Chopin, Philippe; Briley, Mike
CORPORATE SOURCE: Cent. Rech. Pierre Fabre, Castres, F-81106, Fr.
SOURCE: Psychopharmacology (Berlin, Germany) (1992), 106(1), 26-30
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amnesia can be induced in rats in the passive avoidance paradigm by administration of scopolamine, a central muscarinic receptor antagonist. Tacrine or galanthamine, inhibitors of acetylcholinesterase, given in conjunction with scopolamine partially reversed the scopolamine-induced deficit in passive avoidance performance. Four so-called cognitive enhancers, all widely used for the treatment of the symptoms associated with mental aging, cerebral insufficiency and senile memory disorder, were investigated in this paradigm. Piracetam, an extract of Ginkgo biloba, dihydroergocristine and a combination of raubasine with dihydroergocristine, all attenuated the amnesia induced by scopolamine. In contrast, nicergoline had no significant effect. Raubasine alone also failed to attenuate scopolamine-induced amnesia, although some doses of raubasine had a tendency to reduce the amnesia.
IT 321-64-2
RL: BIOL (Biological study)
(scopolamine-induced amnesia response to, cognition enhancers in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



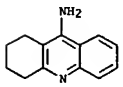
L11 ANSWER 147 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:83569 HCAPLUS
DOCUMENT NUMBER: 116:83569
TITLE: Synthesis and biological activity of galanthamine derivatives as acetylcholinesterase (AChE) inhibitors
AUTHOR(S): Han, So Yeop; Mayer, Scott C.; Schweiger, Edwin J.; Davis, Bonnie M.; Joullie, Madeleine M.
CORPORATE SOURCE: Dep. Chem., Univ. Pennsylvania, Philadelphia, PA, 19104-6323, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1991), 1(11), 579-80
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The syntheses of several ester and carbamate derivs. of galanthamine are described. These compds. are potential therapeutic agents in the treatment of Alzheimer's disease. The inhibition of cortical acetylcholinesterase (AChE) by these drug candidates with different side chains was investigated. Side chain length as well as branching affected the AChE inhibitory activity. Esters were generally less effective than carbamates.
IT 138963-40-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and inhibition by, of acetylcholine esterase)
RN 138963-40-3 HCAPLUS
CN Galanthamine, propylcarbamate (ester) (9CI) (CA INDEX NAME)



L11 ANSWER 148 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:76295 HCAPLUS
DOCUMENT NUMBER: 116:76295
TITLE: Evaluation of a cholinomimetic drug, 9-amino-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]quinoline (NIK-247), as an enhancer of endogenous efflux of acetylcholine from brain slices
AUTHOR(S): Ishii, Y.; Sumi, T.
CORPORATE SOURCE: Dep. Psychopharmacol., Psychiatr. Res. Inst. Tokyo, Tokyo, 156, Japan
SOURCE: Neuropharmacology (1992), 31(1), 61-6
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Basal and high-K+-stimulated efflux of endogenous acetylcholine (ACh) from rat brain slices was measured to evaluate the cholinomimetic effect of NIK-247 on the central nervous system. NIK-247 concentration-dependently accelerated the efflux of ACh from slices of striatum.
This drug was nearly twice as potent as 9-amino-1,2,3,4-tetrahydroacridine but had the same potency as physostigmine in enhancing basal efflux, although there was no difference between the efficacy of these drugs in enhancing the K+-stimulated efflux. Both basal and 50 mM K+-stimulated effluxes of ACh were increased by NIK-247, not only from the striatum but also from slices of the frontal cortex and hippocampus. The drug was more effective in the striatum than in the other tissues, and more effective on K+-stimulated than on basal efflux, regardless of the region of the brain. These effects of NIK-247 may be a result mainly of its inhibition of cholinesterase, and its other biol. characteristics, such as K+ channel blockade, capable of modulating the release of ACh, may not be of major importance.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(acetylcholine efflux from brain regions stimulation by NIK-247 and)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

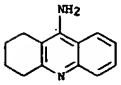


L11 ANSWER 149 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:51413 HCAPLUS
DOCUMENT NUMBER: 116:51413
TITLE: Muscarinic receptor function and acetylcholinesterase activity after chronic admnistration of Tacrine to mice at therapeutic drug concentrations
AUTHOR(S): Kiefer-Day, Jennifer S.; El-Fakahany, Esam E.
CORPORATE SOURCE: Sch. Pharm., Univ. Maryland, Baltimore, MD, USA
SOURCE: Pharmacology (1992), 44(2), 71-80
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors administered 9-amino-1,2,3,4-tetrahydroacridine (THA, Tacrine) to mice in doses (0.3-3 mg/kg) which have been shown to enhance cognition. Animals were sacrificed at various time points and several markers of cholinergic function were measured. Following 3 mg/kg THA, drug levels in brain were sufficient to inhibit 78-80% of brain acetylcholinesterase activity, regardless of treatment duration. However, repeated administration of THA did not alter the number of muscarinic receptors of the phosphoinositide response to muscarinic receptor agonists. Thus, at therapeutically relevant doses, THA inhibits the activity of brain acetylcholinesterase substantially, but does not affect the d. of muscarinic receptors on their ability to activate second messenger systems. These results are in contrast to those obtained by other investigators who found significant decreases in muscarinic receptor number following chronic administration of higher doses of THA.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(Alzheimer's disease treatment by, muscarinic receptor and acetylcholinesterase activity in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



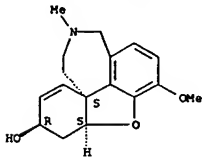
L11 ANSWER 150 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:670625 HCAPLUS
DOCUMENT NUMBER: 115:270625
TITLE: Muscarinic subtype selectivity of tetrahydroaminoacridine: possible relationship to its capricious efficacy
AUTHOR(S): Kiefer-Day, Jennifer S.; Campbell, Hope E.; Towles, Joseph; El-Fakahany, Esam E.
CORPORATE SOURCE: Sch. Pharm., Univ. Maryland, Baltimore, MD, 21201, USA
SOURCE: European Journal of Pharmacology (1991), 203(3), 421-3
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine discriminated slightly in its potency to displace [3H]N-methylscopolamine ([3H]NMS) binding from different muscarinic receptor subtypes (M2 > M1 > M3) and to allosterically decelerate ligand binding (M2 ≥ M1 > M3). The steep displacement curves suggest that marked changes in receptor occupancy may occur within a relatively narrow dose range. Thus, individual inter-patient variability and inconsistent results in clin. studies may be related to blockade of muscarinic receptors, which would oppose the beneficial effects resulting from acetylcholinesterase inhibition.
IT 321-64-2
RL: BIOL (Biological study)
(muscarinic subtype selectivity of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 151 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:653281 HCAPLUS
DOCUMENT NUMBER: 115:253281
TITLE: Combination of atipamezole and tetrahydroaminoacridine/pilocarpine treatment suppresses high voltage spindle activity in aged rats
AUTHOR(S): Riekkinen, P., Jr.; Riekkinen, M.; Jakala, P.; Sirvio, J.; Lammintausta, R.; Riekkinen, P.
CORPORATE SOURCE: Dep. Neurol., Univ. Kuopio, Kuopio, SF-70211, Finland
SOURCE: Brain Research Bulletin (1991), 27(2), 237-9
CODEN: BRBUDU; ISSN: 0361-9230
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present study evaluated the effects of combined α2-antagonist (atipamezole) and anticholinesterase (tetrahydroaminoacridine, THA) or muscarinic agonist (pilocarpine) treatments on the high voltage spindle (HVS) activity in aged rats. On their own, high doses of THA (3 mg/kg), pilocarpine (3 mg/kg) and atipamezole (3 mg/kg) suppressed HVS activity. Low doses of THA (1 mg/kg), pilocarpine (1 mg/kg) and atipamezole (1 mg/kg) did not suppress HVS activity. Combinations of low doses of atipamezole and THA or pilocarpine suppressed HVS activity. The results suggest that the administration of α2-antagonist blocked the age-related deficit of thalamocortical activation and that a combination of α2-antagonist and a cholinergic drug may more effectively stabilize age-related HVS activity than either of the treatments alone.
IT 321-64-2
RL: BIOL (Biological study)
(as cholinergic agent, combination of α2-adrenergic antagonist and, age-related deficit of brain high voltage spindle activity response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

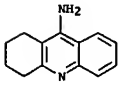


L11 ANSWER 152 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:648005 HCAPLUS
DOCUMENT NUMBER: 115:248005
TITLE: Pharmacokinetics of galanthamine in humans and corresponding cholinesterase inhibition
AUTHOR(S): Bickel, Ulrich; Thomsen, Torben; Weber, Willi; Fischer, Johannes P.; Bachus, Rainer; Nitz, Manfred; Kewitz, Helmut
CORPORATE SOURCE: Inst. Clin. Pharmacol., Free Univ. Berlin, Berlin, 1000/45, Germany
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (1991), 50(4), 420-8
CODEN: CLPTAT; ISSN: 0009-9236
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Measurements were done to determine the plasma concns. of galanthamine and two of its metabolites, as well as the corresponding inhibition of acetylcholinesterase activity in erythrocytes after applying 5 and 10 mg galanthamine hydrobromide as a constant-rate i.v. infusion for 30 min and single oral doses of 10 mg in eight healthy male volunteers. The data obtained revealed first-order pharmacokinetics, complete oral bioavailability, and a mean terminal half-life of 5.68 h. Renal clearance accounted for only 25% of the total plasma clearance (CL = 0.34 L·kg-1). Only negligible quantities of the putative metabolites, epigalanthamine and galanthaminone, were detected in blood and urine. The inhibition of acetylcholinesterase activity was closely correlated with the pharmacokinetics of galanthamine, a median maximal value of 53% being achieved by appling 10 mg galanthamine i.v. Anal. of in vitro and ex vivo concentration responses revealed no differences, indicating that no metabolites of galanthamine exert addnl. inhibition of acetylcholinesterase activity.
IT 357-70-0, Galanthamine
RL: BIOL (Biological study)
(acetylcholinesterase inhibition by and pharmacokinetics of, in humans)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

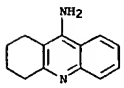
Absolute stereochemistry. Rotation (-).



L11 ANSWER 153 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:598234 HCAPLUS
DOCUMENT NUMBER: 115:198234
TITLE: Tetrahydroaminoacridine and some of its analogs: effects on the cholinergic system
AUTHOR(S): Adem, A.; Mohammed, A.; Nordberg, A.; Winblad, B.
CORPORATE SOURCE: Dep. Geriatr. Med., Karolinska Inst., Stockholm, Swed.
SOURCE: Advances in Behavioral Biology (1990), 38B(Basic, Clin., Ther. Aspects Alzheimer's Parkinson's Dis., Vol. 2), 387-93
CODEN: ADBBBW; ISSN: 0099-6246
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Properties of 9-amino-1,2,3,4-tetrahydroacridine (THA) were examined in vitro and in vivo to define some of the biochem. and behavioral mechanisms by which THA might produce some of its therapeutic effects in Alzheimer's disease. THA had multiple mechanisms of action on the cholinergic system. In addition, the in vitro interactions of 20 THA analogs with cholinergic enzymes and brain muscarinic receptors were also examined
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(cholinergic system response to, Alzheimer's disease in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 154 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:575523 HCAPLUS
DOCUMENT NUMBER: 115:175523
TITLE: The binding of cholinesterase inhibitors tacrine (tetrahydroaminoacridine) and 7-methoxytacrine to muscarinic acetylcholine receptors in rat brain in the presence of eserine
AUTHOR(S): Musilkova, J.; Tucek, S.
CORPORATE SOURCE: Inst. Physiol., Czech. Acad. Sci., Prague, CS-14220, Czech.
SOURCE: Neuroscience Letters (1991), 125(2), 113-16
CODEN: NELEDS; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cholinesterase inhibitor tacrine (1,2,3,4-tetrahydro-9-aminoacridine) is known to interfere with the binding of specific ligands to muscarinic receptors with unusually steep binding inhibition curves. It was investigated whether the concentration dependence of the inhibition of binding is associated with the inhibitory effect of tacrine on the activity of cholinesterases, and the effect of tacrine was compared with that of 7-methoxytacrine. Tacrine inhibited the specific binding of [3H]quinuclidinyl benzilate (QNB) in rat brain cortex with IC50 values of 11 μM both in the absence and in the presence of 100 μM eserine, which had been added to ensure complete inhibition of cholinesterases at all concns. of tacrine; in the cerebellum, the IC50 value was 10 μM in the absence and 14 μM in the presence of eserine; Hill slope factors were in the range of 1.55-1.79 and were not affected by the presence of eserine. 7-Methoxytacrine inhibited the binding of [3H]QNB with an IC50 value of 2.3 μM in the cortex and of 2.6 μM in the cerebellum. The results indicate that the degree and the steep course of the inhibition of [3H]QNB binding to M1 and M2 muscarinic receptors by tacrine do not depend on its inhibitory effect on cholinesterases, and that 7-methoxytacrine is likely to interfere with the function of muscarinic receptors 4-5 times more strongly than tacrine.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(binding of, by muscarinic receptors of brain cerebellum and cerebral cortex, cholinesterase inhibition in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 155 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:558930 HCAPLUS
DOCUMENT NUMBER: 115:158930
TITLE: Synthesis of carbon-11 labeled 9-[11C]methylamino-1,2,3,4-tetrahydroacridine, a potent acetylcholine esterase inhibitor
AUTHOR(S): Bonnot, S.; Prenant, C.; Crouzel, C.
CORPORATE SOURCE: Serv. Hosp. Frederic Joliot, Orsay, 91406, Fr.
SOURCE: Applied Radiation and Isotopes (1991), 42(7), 690-1
CODEN: ARISEF; ISSN: 0883-2889
DOCUMENT TYPE: Journal
LANGUAGE: English
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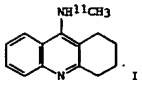
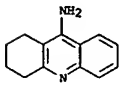
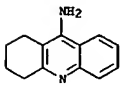


AB A method is described by which 3.7 GBq (100 mCi) of a derivative of tetrahydroaminoacridine (THA) N-[11C]methylTHA (I) was obtained from about 55 GBq (1.5 Ci) of 11CO2. THA was methylated with 11CH3I after deprotonation by NaH in DMSO at 100°. The specific activity avs. 35 GBq/μmol (950 mCi/μmol) at the end of synthesis (total time of synthesis: 45 min from EOB).
IT 321-64-2, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: RCT (Reactant); RACT (Reactant or reagent)
(methylation of, with carbon-11-labeled Me iodide in sodium hydride presence in DMSO)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

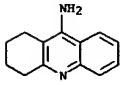


L11 ANSWER 156 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:526185 HCAPLUS
DOCUMENT NUMBER: 115:126185
TITLE: Tacrine: a pharmacological review
AUTHOR(S): Freeman, Shirley E.; Dawson, R. M.
CORPORATE SOURCE: Mater. Res. Lab., DSTO, Melbourne, 3032, Australia
SOURCE: Progress in Neurobiology (Oxford, United Kingdom) (1991), 36(4), 257-77
CODEN: PGNBA5; ISSN: 0301-0082
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 162 refs. on tacrine interactions with morphine, with drugs that block the myoneural junction, with glycolate psychotomimetic drugs, with cholinesterases, with muscarinic receptors, with ion channels, with the release and uptake of neurotransmitters, and use as an antidote against nerve agent poisoning and in Alzheimer's disease.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(pharmacol. and uses of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 157 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:505895 HCAPLUS
DOCUMENT NUMBER: 115:105895
TITLE: Modulation of EEG rhythmicity and spike activity in the rat hippocampus by systemically administered tetrahydroaminoacridine, scopolamine and atipamezole
AUTHOR(S): Valjakka, Antti; Lukkarinen, Keijo; Koivisto, Esa; Riekkinen, Paavo, Jr.; Miettinen, Riitta; Airaksinen, Mauno M.; Lammintausta, Risto; Riekkinen, Paavo
CORPORATE SOURCE: Dep. Neurol., Univ. Kuopio, Kuopio, SF-70211, Finland
SOURCE: Brain Research Bulletin (1991), 26(5), 739-45
CODEN: BRBUDU; ISSN: 0361-9230
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hippocampal EEG recording electrodes were implanted bilaterally in the hilus of the dentate gyrus (DG) and the stratum radiatum layer of the CA1 area in young (2-3-mo-old) and aged (17-20-mo-old) rats. In the subgroups of rats, brain noradrenaline (NA) was depleted by DSP-4 neurotoxin (50 mg/kg, i.p.). The aged animals were included in DSP-4-lesioned group in order to diminish the plastic regeneration of the noradrenergic system which may be more effective in young subjects. All the EEG recordings, after the administration of different agents or vehicle, were made while rats were awake and immobile. Approx. 40% decrease of brain NA had no noticeable effects on the nonrhythmical hippocampal EEG in either age group. In all the rats, compared to the baseline recordings, scopolamine hydrobromide (2 mg/kg, i.p., a muscarinic antagonist) increased the incidence of spontaneous EEG spikes, while tetrahydroaminoacridine (THA, 12.5 mg/kg, i.p., an acetylcholine esterase inhibitor) decreased the spike activity and induced theta rhythm. Atipamezole (3 mg/kg, s.c.), a noradrenergic α2-antagonist, increased the baseline amplitude of the nonrhythmical EEG in the DG and increased slightly the spike activity in the CA1 area. The combined blockade of muscarinic receptors by scopolamine (2 mg/kg) and noradrenergic α2-receptors by atipamezole (3 mg/kg) resulted in irregular EEG pattern and corresponding power spectra differed from the scopolamine spectra. The last combination treatment suggests that the effect of atipamezole was not mediated by the secondary cholinergic activation. In the DG, the spectral power increase caused by atipamezole may be related to the increased excitability/bursting liability of granular cells because NA turnover is increased by this agent and NA increases the excitability of granular cells. Also, the present experiment quant. established that the pattern of the awake immobility-related nonrhythmical EEG is altered by systemically administered scopolamine. Moreover, these pharmacol. manipulations established that the degree of activation of the central muscarinic receptors effectively regulates the relative proportion of the coincidently measured spike activity and EEG rhythmicity in the rat hippocampus. Finally, the results suggest that, in addition to several other electrophysiol. properties, the nonrhythmical EEG activity in the dentate gyrus is influenced by the noradrenergic system.
IT 321-64-2
RL: BIOL (Biological study)
(hippocampal EEG rhythmicity and spike activity response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 157 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 158 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:492098 HCAPLUS
DOCUMENT NUMBER: 115:92098
TITLE: Preparation and formulation of 2-(dimethylamino)ethyl tetrahydroacridinecarboxylates and analogs for treating Alzheimer's disease
INVENTOR(S): Morton, Oswald; Frost, George Thomas Baxter
PATENT ASSIGNEE(S): Trifree Ltd., UK
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9101974	A1	19910221	WO 1990-GB1187	19900731
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RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
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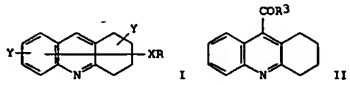
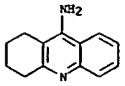
WO 1990-GB1187 A 19900731
OTHER SOURCE(S): MARPAT 115:92098
GI

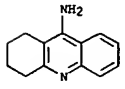


AB The title compds. (I; R = CO2CH2CH2NMe2; X = bond, NR1Z, NHCO2; R1 = H, ZR; Y = H, NH2, NO2, alkyl, alkenyl; Z = bond, divalent organic group) were prepared as acetylcholinesterase inhibitors and as cholinergic agonists (no data). Thus, isatin was refluxed 12 h with cyclohexanone in alc. KOH and the product treated with (COCl)2 to give acridinecarbonyl chloride II (R3 = Cl) which was condensed with Me2NCH2CH2OH to give II.HCl (R3 = OCH2CH2NMe2).
IT 321-64-2P, Tacrine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of acetylcholine esterase inhibitors and cholinergic agonist)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

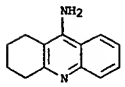
L11 ANSWER 158 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



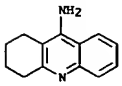
L11 ANSWER 159 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:441759 HCAPLUS
DOCUMENT NUMBER: 115:41759
TITLE: Effects of various cholinomimetic agents on passive avoidance behavior in the nucleus basalis lesioned rats
AUTHOR(S): Simonic, A.; Zupan, Gordana; Domino, E. F.
CORPORATE SOURCE: Dep. Pharmacol., Fac. Med., Rijeka, Yugoslavia
SOURCE: Iugoslavica Physiologica et Pharmacologica Acta (1990), 26(1), 267-74
CODEN: IPPABX; ISSN: 0021-3225
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A hypocholinergic animal model of Alzheimer's disease was developed by producing bilateral electrolytic lesions of the nucleus basalis (NB) in rats. Brain lesioned rats demonstrated significant impairment of passive avoidance compared to control animals both drug naive, without lesions and sham-operated animals. The acetylcholine (ACh) precursor lecithin (3.2·10-4 mol·kg-1 i.p.) and the muscarinic agonist arecoline (6.4·10-6 mol·kg-1 i.p.) significantly improved passive avoidance in the NB lesioned rats. The acetylcholine inhibitors physostigmine (3·10-7 mol·kg-1 i.p.), galanthamine (3.4· 10-6 mol·kg-1 i.p.), and tetrahydroaminoacridine (THA) (5·10-6 mol·kg-1 i.p.) were ineffective in reversing the memory deficits in the NB lesioned rats.
IT 321-64-2
RL: BIOL (Biological study)
(Alzheimer's disease response to, in animal model)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



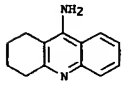
L11 ANSWER 160 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:422939 HCAPLUS
DOCUMENT NUMBER: 115:22939
TITLE: Cholinergic modulation of spatial learning in mice in a Morris-type water maze
AUTHOR(S): Lamberty, Y.; Gower, A. J.
CORPORATE SOURCE: UCB, Braine-l'Alleud, B-1420, Belg.
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie (1991), 309, 5-19
CODEN: AIPTAK; ISSN: 0003-9780
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Injection of the centrally active muscarinic antagonist scopolamine i.p. 20 min pre-test at 3 mg/kg, but not at 1 mg/kg, impaired spatial learning of mice in a Morris-type water maze adapted for mice. Both doses caused hyperactivity. d-Amphetamine (3 mg/kg, i.p.), which also caused hyperactivity, did not impair spatial learning nor did methylscopolamine (3 mg/kg, i.p.). In a cued version of the water maze, apart from a temporary disturbance on day 1, scopolamine (3 mg/kg) and control groups behaved similarly, indicating that scopolamine-induced place learning deficits are not due to changes in swimming ability, motivation, or ability to use proximal cues. Physostigmine (0.1 and 0.2 mg/kg, i.p.) and oxotremorine (0.02 mg/kg but not 0.01 mg/kg, i.p.) antagonized the deficits in the swimming maze. Neither drug affected the scopolamine hyperactivity despite causing hypoactivity per se. In contrast, the peripherally acting cholinergic drug neostigmine was inactive against scopolamine in either test at 0.1 mg/kg. THA (2-8 mg/kg, i.p.), RS 86 (0.25-1 mg/kg, i.p.), and nicotine (1 and 3 mg/kg, i.p.) were also unable to antagonize the scopolamine effect. These studies show that scopolamine disrupts acquisition of spatial rather than cued learning in mice in a Morris-type water maze and that this effect appears to be mediated centrally and can be dissociated from drug-induced hyperactivity. Moreover, this deficit can be reversed with certain cholinergic agents.
IT 321-64-2, THA
RL: BIOL (Biological study)
(spatial learning response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



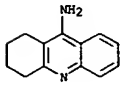
L11 ANSWER 161 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:422035 HCAPLUS
DOCUMENT NUMBER: 115:22035
TITLE: Correlation between blood and tissue levels of tetrahydroaminoacridine, cholinesterase inhibition, and acetylcholine increase in the brain
AUTHOR(S): Pleul, O.; Rost, L.; Thomsen, T.; Weber, W.; Kewitz, H.
CORPORATE SOURCE: Inst. Clin. Pharmacol., Free Univ. Berlin, Berlin, D-1000/45, Fed. Rep. Ger.
SOURCE: Klinische Pharmakologie (1989), 2(Pharmacol. Interventions Cent. Cholinergic Mech. Senile Dementia (Alzheimer's Dis.)), 292-7
CODEN: KLPHEH; ISSN: 0937-0978
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this paper the authors describe the time course and the tissue distribution of tetrahydroaminoacridine (THA) at various doses and the corresponding inhibition of ChE. There was a slight preference of THA for butyrylcholinesterase in comparison to acetylcholinesterase in vivo. Therefore, the estimation of acetylcholinesterase in red blood cells may serve
better than the plasma esterase to indicate esterase inhibition in brain in vivo which is important in monitoring the therapeutic effect of THA in man. The observed slight differences between the THA effects on erythrocytes
and brain can be neglected for therapeutic decisions.
IT 321-64-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, in relation to cholinesterase inhibition and brain acetylcholine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



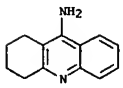
L11 ANSWER 162 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:422034 HCAPLUS
DOCUMENT NUMBER: 115:22034
TITLE: Inhibition of acetyl- and butyrylcholinesterase as induced by various reversible enzyme inhibitors in vitro
AUTHOR(S): Thomsen, T.; Zendeh, B.; Bickel, U.; Kewitz, H.
CORPORATE SOURCE: Inst. Clin. Pharmacol., Free Univ. Berlin, Berlin, D-1000/45, Fed. Rep. Ger.
SOURCE: Klinische Pharmakologie (1989), 2(Pharmacol. Interventions Cent. Cholinergic Mech. Senile Dementia (Alzheimer's Dis.)), 284-7
CODEN: KLPHEH; ISSN: 0937-0978
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reversible cholinesterase inhibitors have been reported to provide beneficial effects in Alzheimer's disease. One possible mechanism might be the restoration of the cholinergic deficit by modulation of brain acetylcholine levels. The purpose of this investigation was to compare the acetyl- and butyrylcholinesterase inhibition in vitro of 4 different reversible enzyme inhibitors in clin. use.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholinesterase and butylcholinesterine activity in human blood response to, Alzheimer's in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



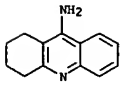
L11 ANSWER 163 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:422033 HCAPLUS
DOCUMENT NUMBER: 115:22033
TITLE: Interaction of tetrahydroaminoacridine with cholinergic systems in vitro and in vivo
AUTHOR(S): Cross, A. J.; DeSouza, R. J.; Murray, T. K.; Robinson, T. N.; Green, A. R.
CORPORATE SOURCE: Astra Neurosci. Res. Unit, London, WC1N 1PJ, UK
SOURCE: Klinische Pharmakologie (1989), 2(Pharmacol. Interventions Cent. Cholinergic Mech. Senile Dementia (Alzheimer's Dis.)), 278-9
CODEN: KLPHEH; ISSN: 0937-0978
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study the authors examined the effects of tetrahydroaminoacridine (THA) on cholinergic systems in vitro and in vivo. THA is a potent reversible AChE inhibitor, which interacts with muscarinic receptors at high concns. THA does not enhance the release of ACh either in vivo or in vitro. It is likely, therefore, that the cholinergic actions of THA can be explained solely on the basis of AChE inhibition.
IT 321-64-2
RL: BIOL (Biological study)
(cholinergic system response to, in cerebral cortex)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 164 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:400696 HCAPLUS
DOCUMENT NUMBER: 115:696
TITLE: Reversal of learning impairment in ventral globus pallidus-lesioned rats by combination of continuous intracerebroventricular choline infusion and oral cholinergic drug administration
AUTHOR(S): Ueki, Akinori; Miyoshi, Koho
CORPORATE SOURCE: Dep. Neuropsychiatry, Hyogo Coll. Med., Nishinomiya, 663, Japan
SOURCE: Brain Research (1991), 547(1), 99-109
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of sep. or combined oral administration of THA (9-amino-1,2,3,4-tetrahydroacridine hydrochloride) and NIK-247 (9-amino-2,3,6,7,8-hexahydro-1H-cyclopenta[b] quinoline monohydrate hydrochloride) and intracerebroventricular choline infusion using an osmotic minipump were investigated by observing locomotor activity, shock sensitivity, passive avoidance response and cerebral choline and acetylcholine contents in the bilateral ventral globus pallidus-lesioned rat. Evaluation of locomotor activity and shock sensitivity revealed no sensorimotor disturbances caused by combined administration. Intracerebroventricular choline infusion (100 μmol/day) and oral THA or NIK-247 administration (0.5 mg/kg) and intracerebroventricular choline infusion (100 μmol/day) elicited good acquisition of passive avoidance learning and produced a significant increase of choline and acetylcholine in the cerebral cortex of the bilateral ventral globus pallidus-lesioned rat. These findings suggest that continuous intracerebroventricular choline infusion may intensify the ameliorating effect of THA or NIK-247 on learning disturbance.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(learning impairment reversal by intracerebroventricular choline and oral, in ventral globus pallidus lesions)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

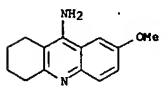


L11 ANSWER 165 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:221294 HCAPLUS
DOCUMENT NUMBER: 114:221294
TITLE: Effects of tacrine, velnacrine (HP029), suronacrine (HP128), and 3,4-diaminopyridine on skeletal neuromuscular transmission in vitro
AUTHOR(S): Braga, M. F. M.; Harvey, A. L.; Rowan, E. G.
CORPORATE SOURCE: Strathclyde Inst. Drug Res., Univ. Strathclyde, Glasgow, G1 1XW, UK
SOURCE: British Journal of Pharmacology (1991), 102(4), 909-15
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tacrine (9-amino-1,2,3,4-tetrahydroacridine), velnacrine (HP029, 9-amino-1,2,3,4-tetrahydroacridin-1-ol maleate), suronacrine (HP128, 9-benzylamino-1,2,3,4-tetrahydroacridin-1-ol maleate), and 3,4-diaminopyridine on neuromuscular transmission were compared on isolated nerve-muscle prepns. Tacrine, HP029, and 3,4-diaminopyridine augmented responses of chick biventer cervicis prepns. to nerve stimulation, with tacrine and HP029 increasing responses to exogenously applied acetylcholine HP128 blocked responses to nerve stimulation and to carbachol, but increased responses to acetylcholine. In mouse diaphragm prepns. that were partially paralyzed by tubocurarine or low calcium solns., tacrine, HP029, and 3,4-diaminopyridine reversed the twitch block. HP128 deepened the block. In mouse triangularis sterni prepns., tacrine and HP029 prolonged the decay phase of endplate potentials and miniature endplate potentials, but had no effect on quantal content at 36°; above 10 μM, they reduced endplate potential amplitude. 3,4-Diaminopyridine increased quantal content without affecting the time course of the endplate potentials. HP128 (1-10 μM) had no effect on amplitude or time course of endplate potentials, but reduced their amplitude at higher concns. Extracellular recording of nerve terminal currents from triangularis sterni prepns. revealed that 3,4-diaminopyridine and HP128 had a selective blocking action on the waveform associated with K+ currents, tacrine reduced and prolonged the K+-related waveform, and HP029 had nonselective blocking actions only seen at high concns. Tacrine and HP029 behave predominantly as anticholinesterase agents, while HP128 has weaker anticholinesterase actions that are masked by cholinoceptor blockade. Tacrine and HP128, but not HP029, have some blocking actions on K+ currents of mouse motor nerve terminals.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(cholinergic actions of, diaminopyridine in comparison with, in effect on neuromuscular transmission)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

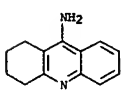


L11 ANSWER 165 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

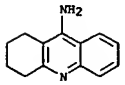
L11 ANSWER 166 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:221166 HCAPLUS
DOCUMENT NUMBER: 114:221166
TITLE: Unexpected potentiating effect of a tacrine derivative (9-amino-7-methoxy-1,2,3,4-tetrahydroacridine) upon the nonepileptic myoclonus in baboons (Papio papio)
AUTHOR(S): Svejdova, Milada; Rektor, Ivan; Silva-Barrat, Carmen; Menini, Christian
CORPORATE SOURCE: Dep. Neurophysiol. Appl., CNRS, Gif-sur-Yvette, Fr.
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1990), 14(6), 961-6
CODEN: PNPPD7; ISSN: 0278-5846
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the title compound, also known as 7-methoxytacrine (7-MEOTA), on the nonepileptic myoclonus of the baboon was studied. This type of myoclonus is thought to depend on a cholinergic system dysfunction, since it can be induced by atropine and blocked by physostigmine. 7-MEOTA is believed to display anticholinesterase activity but it here potentiated the nonepileptic myoclonus occurring either spontaneously or induced by atropine. In baboons not spontaneously presenting nonepileptic myoclonus, 7-MEOTA induced the myoclonus in a fashion similar to that of atropine; such myoclonus was blocked by physostigmine. These data indicate a possible antagonist action of tacrine on the muscarinic acetylcholine receptor. It is suggested that caution is necessary when introducing a tacrine derivative in clin. practice.
IT 5778-80-3, 7-Methoxytacrine
RL: BIOL (Biological study)
(myoclonus potentiation by)
RN 5778-80-3 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-7-methoxy- (9CI) (CA INDEX NAME)



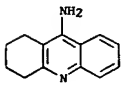
L11 ANSWER 167 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:180015 HCAPLUS
DOCUMENT NUMBER: 114:180015
TITLE: Effect of organophosphorus compounds on the conformation of acetylcholinesterase and acetylcholine receptor
AUTHOR(S): Yang, J. T.; Wu, C. S. C.; Sun, X. H.
CORPORATE SOURCE: Univ. California, San Francisco, CA, USA
SOURCE: Report (1989), Order No. AD-A218492, 106 pp. Avail.: NTIS
From: Gov. Rep. Announce. Index (U. S.) 1990, 90(13), Abstr. No. 034,511
DOCUMENT TYPE: Report
LANGUAGE: English
AB Acetylcholinesterase (AChE) from Torpedo californica was purified on acridine affinity columns. The low salt-soluble globular dimer (G2), the tailed asym. decamer (A12), and its proteolytic tetramer (G4) had similar conformation based on CD. Each subunit had about 40% alpha-helix, 35% Beta-sheet, and 4% Beta-turn. The enzymic activity was optimal at pH 7-8 and dropped to zero at pH below 5 or above 10. However, the protein was not completely unfolded; its CD bands retained 70-80% intensities. Thermal denaturation at pH 7.5 occurred between 30 and 40°; again, the loss of activity was accompanied by only 20-30% reduction in CD intensities. Urea denaturation began at 1M urea; it was protein concentration-
and time-dependent. Thus, the enzyme conformation was relatively stable against denaturation. The detergent-soluble G2 could be reconstituted through dialysis into phosphatidylcholine vesicles with no changes in conformation and activity. At 0.07 ionic strength and a molar lipid/protein ratio of 4000, the solution of the reconstituted enzyme was clear for spectroscopic studies. The binding of DFP to AChE was stoichiometric. The aging of the irreversibly DFP-inhibited G4 had a half-life of 4.2-5 h. Irreversible inactivation of G4 by potent inhibitors, such as soman and tabun, could be slowed by adding reversible inhibitors, such as tacrine and hexamethonium bromide.
IT 321-64-2, Tacrine???
RL: BIOL (Biological study)
(organophosphorus compds. effect on acetylcholinesterase conformation in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 168 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:157147 HCAPLUS
DOCUMENT NUMBER: 114:157147
TITLE: Negative effects of tacrine (tetrahydroaminoacridine) and methoxytacrine on the metabolism of acetylcholine in brain slices incubated under conditions stimulating neurotransmitter release
AUTHOR(S): Tucek, Stanislav; Dolezal, Vladimir
CORPORATE SOURCE: Inst. Physiol., Slovak Acad. Sci., Prague, 14220, Czech.
SOURCE: Journal of Neurochemistry (1991), 56(4), 1216-21
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tacrine (1,2,3,4-tetrahydro-9-aminoacridine) and 7-methoxytacrine on the metaabolism of brain acetylcholine were investigated in expts. in which acetylcholine turnover was stimulated by tissue depolarization or by 4-aminopyridine. In expts. in which [14C]choline was present in the incubation medium simultaneously with tacrine or methoxytacrine, the drugs diminished the uptake of [14C]choline by the tissue and the amount of [14C]acetylcholine synthesized and released into the medium. In these expts., it was not possible to distinguish whether the inhibitory effects of tacrine and methoxytacrine were primarily on thhe process of acetylcholine synthesis (particularly on the uptake of choline), or whether the drugs also acted directly on the process of neurotransmitter release. In subsequent expts. the prisms were preincubated with [14C]choline and only then subjected to a short depolarization in the presence of hemicholinium-3 and tacrine or methoxytacrine. Both drugs severely inhibited the release of preformed [14C]acetylcholine and prevented the diminution of tissue [14C]acetylcholine stores. Methoxytacrine was also found to diminish the release of acetylcholine induced by 4-aminopyridine while increasing the content of acetylcholine in the tissue. Tacrine and methoxytacrine had no effect on the activity of choline acetyltransferase (EC 2.3.1.6). The observations indicate that, in addition to reducing the uptake of choline, tacrine and methoxytacrine inhibit the stimulated release of acetylcholine by acting directly on the process of neurotransmitter liberation.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine metabolism and release inhibition by, in stimulated brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

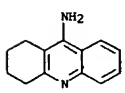


L11 ANSWER 169 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:157146 HCAPLUS
DOCUMENT NUMBER: 114:157146
TITLE: Positive and negative effects of tacrine (tetrahydroaminoacridine) and methoxytacrine on the metabolism of acetylcholine in brain cortical prisms incubated under "resting" conditions
AUTHOR(S): Dolezal, Vladimir; Tucek, Stanislav
CORPORATE SOURCE: Inst. Physiol., Slovak Acad. Sci., Prague, 14220, Czech.
SOURCE: Journal of Neurochemistry (1991), 56(4), 1207-15
CODEN: JONRA9; ISSN: 0022-3042
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tacrine (1,2,3,4-tetrahydro-9-aminoacridine) and 7-methoxytacrine on the metabolism of acetylcholine were investigated in expts. on prisms of rat cerebral cortex incubated in vitro in low-potassium (3 mmol/L K+) media/ cholinesterases were inactivated by paraoxon to avoid any action of tacrine and methoxytacrine via their inhibition. Under "resting" conditions, tacrine and methoxytacrine increased the synthesis of unlabeled acetylcholine in the prisms; at the same time, they inhibited the uptake of [14C]choline from the medium and the synthesis of [14C]acetylcholine. The concentration of free choline was not increased by tacrine or methoxytacrine in either the tissue or the medium. The contradiction between the increased synthesis of unlabeled and the diminished synthesis of labeled acetyllcholine indicates that the utilization of intracellular choline (which is presumably mobilized from intracellular choline esters) for the synthesis of acettylcholine is increased by tacrine and methoxytacrine. This conclusion is supported by the observation that the inhibition of acetylcholine synthesis during incubation with hemicholinium-3 (an inhibitor of choline transport into cholinergic nerve terminals) was overcome when tacrine was present simultaneously with hemicholinium-3. When the prisms were preincubated with [14C]choline and incubated with tacrine or methoxytacrine only after this, the amount of [14C] acetylcholine recovered in the tissue plus the medium was higher at the end of incubation with tacrine or methoxytacrine than without them, again suggesting that the drugs were able to increase the utilization of intracellular [14C]choline or its esters for acetylcholine synthesis.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine metabolism by brain inhibition by, under resting condition)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

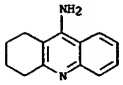


L11 ANSWER 169 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

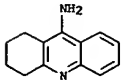
L11 ANSWER 170 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:135961 HCAPLUS
DOCUMENT NUMBER: 114:135961
TITLE: Tetrahydroaminoacridine inhibits high voltage spindle activity in aged rats after acute and chronic treatment
AUTHOR(S): Riekkinen, Paavo, Jr.; Aaltonen, Minna; Riekkinen, Paavo
CORPORATE SOURCE: Dep. Neurol., Univ. Kuopio, Kuopio, SE-70210, Finland
SOURCE: Psychopharmacology (Berlin, Germany) (1991), 103(2), 265-7
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability of tetrahydroaminoacridine (THA) to reverse the age-related increase in EEG high-voltage spindles (HVS) was studied in rats. THA was injected 15 or 90 min before EEG recordings were made. THA at 3 mg/kg i.p. decreased the incidence of HVS, but was ineffective at 0.03 and 1 mg/kg. The HVS-suppressing effect of THA (3 mg/kg) declined during a 10-day treatment period. After 10 days as chronic THA treatment, a challenge dose of 6 mg THA/kg reinstated the HVS suppressing effect of THA. Thus, THA reverses the age-related deficit of thalamo-cortical activation and tolerance develops to THA-induced HVS suppression. An anti-cholinesterase activity may be important for the efficacy of THA in decreasing HVS because pilocarpine, a muscarinic agonist, also decreased HVS.
IT 321-64-2
RL: BIOL (Biological study)
(brain EEG high-voltage spindles inhibition by, in senescence, cholinesterase inhibition in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



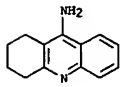
L11 ANSWER 171 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:115023 HCAPLUS
DOCUMENT NUMBER: 114:115023
TITLE: High-affinity [3H]THA (tetrahydroaminoacridine) binding sites in rat brain
AUTHOR(S): Mena, E. Edward; Desai, Manoj C.
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Pharmaceutical Research (1991), 8(2), 200-3
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine (THA), an acetylcholinesterase inhibitor that is reported to have significant effects on cognition and memory in Alzheimer's disease patients, binds to rat brain membranes in a saturable and reversible manner. Computer anal. of the binding data revealed high- and low-affinity sites with Kd values of 97.8 nM and 4.65 μM and Bmax values of 4.13 and 114 pmol/mg protein. Autoradiog. studies show that these binding sites are not colocalized with acetylcholinesterase activity. The binding of [3H]THA to membranes does not appear to be related to receptors for several neurotransmitters/neuromodulators, including acetylcholine and other acetylcholinesterase inhibitors. Amiridin, a closely related acetylcholinesterase inhibitor, was able to block specific [3H]THA binding (IC50 = 1.05 μM). While the function of THA mediated by these sites is unknown, they may be responsible in part for the distinct clin. effects of tetrahydroaminoacridine compared to other acetylcholinesterase inhibitors.
IT 321-64-2
RL: BIOL (Biological study)
(receptors for, in brain, Alzheimer's treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



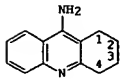
L11 ANSWER 172 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:56218 HCAPLUS
DOCUMENT NUMBER: 114:56218
TITLE: Interactions between scopolamine and muscarinic cholinergic agonists or cholinesterase inhibitors on spatial alternation performance in rats
AUTHOR(S): Shannon, Harlan E.; Bemis, Kerry G.; Hendrix, James C.; Ward, John S.
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1990), 255(3), 1071-7
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects on working memory of the muscarinic cholinergic agonists oxotremorine, arecoline, RS 86, and pilocarpine and the cholinesterase inhibitors physostigmine and tetrahydroaminoacridine were investigated in male F344 rats. Working memory was assessed by behavior maintained under a spatial alternation schedule of food presentation in which the interval between trials was varied from 2 to 32 s. Under control conditions the percentage of correct responses decreased as the retention interval was varied from 2 to 32 s. Administered alone the cholinergic agonists oxotremorine (0.01-0.1 mg/kg), arecoline (3-30 mg/kg), RS 86 (0.3-3 mg/kg), and pilocarpine (0.3-3.0 mg/kg), and the cholinesterase inhibitors physostigmine (0.01-0.1 mg/kg) and tetrahydroaminoacridine (0.3-3.0 mg/kg) either had no effect on or produced dose-related deficits in working memory and decreases in response rates. The muscarinic antagonist scopolamine (0.1 mg/kg) produced retention interval-development decreases in the percentage of correct responding and rates of responding. The cholinergic agonists and tetrahydroaminoacridine failed to reverse the effects of scopolamine. However, physostigmine produced a dose-dependent reversal of the working-memory deficits and response-rate decreasing effects of scopolamine. The results are consistent with the interpretation that drugs which primarily enhance M2 muscarinic cholinergic transmission are ineffective in enhancing working memory or in reversing scopolamine-induced deficits in working memory.
IT 321-64-2
RL: BIOL (Biological study)
(memory nonresponse to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 173 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:35723 HCAPLUS
DOCUMENT NUMBER: 114:35723
TITLE: The effect of tacrine on acetylcholine overflow in the heart
AUTHOR(S): Lindmar, Ruth; Loeffelholz, Konrad
CORPORATE SOURCE: Dep. Pharmacol., Univ. Mainz, Mainz, 6500, Germany
SOURCE: European Journal of Pharmacology (1990), 190(1-2), 251-4
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine, 10-6 M, enhanced the acetylcholine (ACh) overflow evoked in perfused chicken hearts by field stimulation (5 Hz, 1 min) from 183 to 346 pmol/g/min. Increases to the same level were observed after pretreatment with diisopropylfluorophosphate (DFP) as well as after DFP plus 10-6 M tacrine. Tacrine, 10-5 M, caused further enhancement with or without DFP up to 851 pmol/g/min. It was concluded that 10-6 M tacrine enhanced the ACh overflow by choline esterase inhibition, whereas 10-5 M tacrine caused, in addition, an increase of neuronal ACh release.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(heart acetylcholine release increase by, concentration in relation to, cholinesterase inhibition role in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

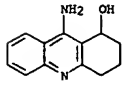


L11 ANSWER 174 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:17048 HCAPLUS
DOCUMENT NUMBER: 114:17048
TITLE: Identification of the urinary metabolites of tacrine in the rat
AUTHOR(S): Hsu, Robert S.; Shutske, Gregory M.; Dileo, Eva M.; Chesson, Susan M.; Linville, Anastasia R.; Allen, Richard C.
CORPORATE SOURCE: Chem. Res. Dep., Hoechst-Roussel Pharm., Somerville, NJ, USA
SOURCE: Drug Metabolism and Disposition (1990), 18(5), 779-83
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

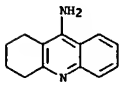


I

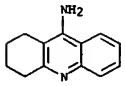
AB Tacrine (I, THA) is a potent cholinesterase inhibitor for the treatment of Alzheimer disease. The metabolism and excretion of THA were studied in rats following a single oral dose of 20 mg/kg. THA was extensively metabolized. Three major urinary metabolites were isolated by HPLC using a semi-preparative anal. Ph column and subsequent purification of individual fractions on a cyano column. The major metabolic pathways involve hydroxylation of the saturated ring at positions 1,2, and 4. The structures of the metabolites 9-amino-1,2,3,4-tetrahydroacridin-1-ol (1-OH-THA), 9-amino-1,2,3,4-tetrahydroacridin-2-ol (2-OH-THA), and 9-amino-1,2,3,4-tetrahydroacridin-4-ol (4-OH-THA) were determined by electron impact mass spectrometry and/or 1H-NMR. The urinary excretion of THA and metabolites was quantitated by HPLC with UV-detection. About 60% of the oral dose was eliminated as total THA, 1-OH-THA, 2-OH-THA, and 4-OH-THA over a 48-h collection interval. The non-conjugated THA and hydroxylated metabolites accounted for 45% of the dose.
IT 124027-47-0, 9-Amino-1,2,3,4-tetrahydroacridin-1-ol
RL: FORM (Formation, nonpreparative)
(formation of, as tacrine metabolites, in urine)
RN 124027-47-0 HCAPLUS
CN 1-Acridinol, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



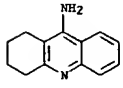
L11 ANSWER 175 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:605292 HCAPLUS
DOCUMENT NUMBER: 113:205292
TITLE: Tetrahydroaminoacridine induces opposite changes in muscarinic and nicotinic receptors in rat brain
AUTHOR(S): Nilsson-Hakansson, Lena; Lai, Zhennan; Nordberg, Agneta
CORPORATE SOURCE: Dep. Pharmacol., Univ. Uppsala, Uppsala, S-751 24, Swed.
SOURCE: European Journal of Pharmacology (1990), 186(2-3), 301-5
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rats were treated with the acetylcholinesterase inhibitor tetrahydroaminoacridine (THA) twice daily for 14 days. THA (10 mg/kg) induced a decrease in the number of muscarinic receptors (both M1 and M2) in the cortex and striatum, whereas the number of nicotinic receptors in the cortex and hippocampus increased. Rats treated with physostigmine (0.9 mg/kg) showed a reduced number of muscarinic receptors, but no change in nicotinic receptors. Thus, treatment with cholinesterase inhibitors can induce opposite changes in brain muscarinic and nicotinic receptors in vivo.
IT 321-64-2
RL: BIOL (Biological study)
(muscarinic and nicotinic receptors of brain regions response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 176 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:605249 HCAPLUS
DOCUMENT NUMBER: 113:205249
TITLE: Effects of repeated administration of tetrahydroaminoacridine (THA) on muscarinic receptor subtypes in the rat brain
AUTHOR(S): Alonso, R.; Kan, J. P.; Worms, P.; Soubrie, P.
CORPORATE SOURCE: Dep. Neuropsychiatry, Sanofi Rech., Montpellier, 34082, Fr.
SOURCE: Neurochemistry International (1990), 17(3), 457-65
CODEN: NEUIDS; ISSN: 0197-0186
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of a chronic treatment (21 days) with the acetylcholinesterase (AChE) inhibitor tetrahydroaminoacridine (THA) on muscarinic receptors subtypes were investigated at various times after the last administration of the drug, in various brain areas including cortex, striatum, hippocampus and cerebellum. Forty eight hours after the end of chronic THA treatment, the number of muscarinic receptors, labeled with [3H]NMS, was significantly lowered in the cortex and the striatum, but not in the hippocampus or cerebellum. High affinity pirenzepine binding sites (M1 receptors), directly assayed using [3H]pirenzepine saturation assays or estimated by pirenzepine-[3H]NMS competition, were lowered only in the cortex and in the striatum of THA-treated rats. In contrast, the number of low affinity pirenzepine sites (M2 receptors), was not significantly modified. At shorter wash-out period (18 h), the d. of M1 receptors decreased by 26, 46 and 52% in the hippocampus, cerebral cortex and striatum, resp. In all cases, Kd values remained unchanged suggesting that the loss of M1 sites was not due to a modification of radioligand affinity for the receptors. Although THA displayed a micromolar affinity for M1 and M2 receptors in vitro, this AChE inhibitor did not interfere with the receptor assays since no trace of residual free THA was detected in rat brain at 48 h post-treatment. These results suggest that chronic treatment with THA produced a selective down-regulation of M1 receptors; they also indicate that these receptors may be regulated differently in cortical, striatal, hippocampal or cerebellar regions.
IT 321-64-2
RL: BIOL (Biological study)
(muscarinic receptor subtypes of brain regions response to chronic administration of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



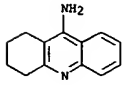
L11 ANSWER 177 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:604748 HCAPLUS
DOCUMENT NUMBER: 113:204748
TITLE: Effects of tetrahydro-9-aminoacridine on cortical and hippocampal neurons in the rat: an in vivo and in vitro study
AUTHOR(S): Dutar, P.; Bassant, M. H.; Lamour, Y.
CORPORATE SOURCE: INSERM, Paris, Fr.
SOURCE: Brain Research (1990), 527(1), 32-40
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tetrahydro-9-aminoacridine (THA), an anticholinesterase drug, have been studied in the rat both in vivo (cerebral cortex) and in vitro (CA1 field of the hippocampus) and compared with those of physostigmine. In the cerebral cortex, THA potentiated the excitatory effect of acetylcholine in most neurons, including cortical neutrons recorded from chronic unanesthetized animals. In vitro, THA (but not physostigmine) had a depolarizing, atropine- and tetrodotoxin-insensitive effect. This effect is associated with an increase in membrane resistance which suggests a direct effect of THA on hippocampal neurons. In addition, THA blocked the slow inhibitory postsynaptic potential. At the same concentration, THA potentiated the slow cholinergic excitatory postsynaptic potential produced by elec. stimulation of the cholinergic afferents. Its potency was, however, about 10 times lower than that of physostigmine. These results show that THA: (1) is an anticholinesterase much less potent than physostigmine; but (2) which has also direct effects on central neurons which are not observed with physostigmine and are unrelated to its anticholinesterase activity.
IT 321-64-2
RL: BIOL (Biological study)
(brain cortex and hippocampus response to, Alzheimer's treatment in relation to, anticholinesterase activity in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



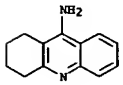
L11 ANSWER 178 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:584728 HCAPLUS
DOCUMENT NUMBER: 113:184728
TITLE: Synergistic drugs for treating neurological disorders comprising a potassium channel blocker and a choline source
INVENTOR(S): Wurtman, Richard J.; Buyukuysal, Rifat Levent
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 8909600	A1	19891019	WO 1989-US1402		19890404
W: JP					
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
EP 408650	A1	19910123	EP 1989-904963		19890404
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE					
JP 03505868	T2	19911219	JP 1989-504758		19890404
PRIORITY APPLN. INFO.:			US 1988-179590	A	19880408
			WO 1989-US1402	W	19890404

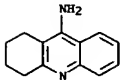
AB Compns. comprising choline, or a choline source, and a K channel blocker are synergistic drugs for the treatment of neurol. degenerative disorders which affect cholinergic neurons (no data). A mixture of 20 μM choline and 50 μM 4-aminopyridine synergistically released acetylcholine from the rat brain striatum, in vitro.
IT 321-64-2D, mixts. with potassium channel blockers
RL: BIOL (Biological study)
(drugs containing, for treatment of neurol. disorders, synergistic)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



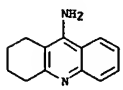
L11 ANSWER 179 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:584640 HCAPLUS
DOCUMENT NUMBER: 113:184640
TITLE: Inhibition of rat brain histamine-N-methyltransferase by 9-amino-1,2,3,4-tetrahydroacridine (THA)
AUTHOR(S): Cumming, Paul; Reiner, Peter B.; Vincent, Steven R.
CORPORATE SOURCE: Dep. Psychiatry, Univ. British Colombia, Vancouver, BC, V6T 1W5, Can.
SOURCE: Biochemical Pharmacology (1990), 40(6), 1345-50
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 9-Amino-1,2,3,4-tetrahydroacridine (THA), an inhibitor of acetylcholinesterase, has been proposed as a treatment for Alzheimer's disease on the basis of its ability to increase cerebral levels of acetylcholine. THA shares structural features with aminoquinoline compds. known to be inhibitors of histamine-N-methyltransferase (HNMT). THA was found to be a potent competitive inhibitor of rat brain HNMT in vitro, with a Ki of 35 nM with respect to both histamine and S-adenosyl-L-methionine, the co-substrate. Two hours after systemic administration of THA (5 and 10 mg/kg, i.p.), HNMT from rat brain was largely inhibited. The levels of histamine in striatum and cerebral cortex were elevated by this treatment. Thus, THA at moderate doses is able to alter histamine metabolism in the central nervous system.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(histamine methyltransferase inhibition by, in brain, histamine metabolism in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



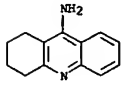
L11 ANSWER 180 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:545259 HCAPLUS
DOCUMENT NUMBER: 113:145259
TITLE: Tetrahydroaminoacridine increases acetylcholine synthesis and glucose oxidation by mouse brain slices in vitro
AUTHOR(S): Peterson, Christine
CORPORATE SOURCE: Dep. Psychobiol., Univ. California, Irvine, CA, 92717, USA
SOURCE: Neuroscience Letters (1990), 115(2-3), 274-8
CODEN: NELEDS; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1,2,3,4-Tetrahydro-5-aminoacridine (THA; tacrine), which reportedly improves cognitive deficits in certain individuals with Alzheimer's disease, increased glucose oxidation and acetylcholine (ACh) synthesis by mouse brain slices. THA increased [U-14C]glucose decarboxylation and ACh formation in a concentration-dependent manner in hippocampal slices (50 nM < 50 μM < 500 μM). In striatal and cortical slices, 50 μM THA elevated the oxidation of glucose and its incorporation into ACh. Thus, the efficacy of THA treatment on Alzheimer patients may be partially related to increased ACh synthesis and oxidative metabolism
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine formation and glucose oxidation by brain regions response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



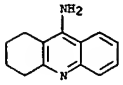
L11 ANSWER 181 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:491893 HCAPLUS
DOCUMENT NUMBER: 113:91893
TITLE: Effect of nicotine and tacrine on acetylcholine release from rat cerebral cortical slices
AUTHOR(S): Loiacono, R. E.; Mitchelson, F. J.
CORPORATE SOURCE: Sch. Pharmacol., Victorian Coll. Pharm., Parkville, 3052, Australia
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1990), 342(1), 31-5
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of nicotine (1-10 μM) and tacrine on stimulation-evoked release of [3H]acetylcholine from the rat brain slice preparation preincubated with [3H]choline was investigated. In these prepns., nicotine enhanced but tacrine inhibited evoked [3H]acetylcholine release. These effects were blocked by (+)tubocurarine (1 μM) and atropine (0.1 μM), resp. In the presence of idazoxan (0.3 μM) plus atropine (0.1 μM), nicotine (3 μM) continued to enhance-evoked [3H] acetylcholine release, but the inhibitory effect of tacrine (1 μM) on evoked [3H] acetylcholine release was reversed to an enhancement. Under these circumstances the effects of both nicotine and tacrine were blocked by (+)tubocurarine (1 μM). Thus, tacrine can both inhibit or enhance [3H]acetylcholine release, most likely through its activity as a cholinesterase inhibitor. Under normal circumstances following tacrine the predominant effect of the elevated levels of acetylcholine will be activation of inhibitory presynaptic muscarine receptors on cholinergic nerves and an inhibition of evoked [3H]acetylcholine release. Under conditions where both presynaptic inhibitory muscarine and α2-adrenoceptors are blocked, the elevated levels of acetylcholine produced by tacrine will lead to the activation of facilitatory presynaptic nicotine cholinoceptors on cholinergic nerves and an enhancement of evoked [3H] acetylcholine release.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine release by cerebral cortex response to, nicotine and its receptors in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 182 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:491392 HCAPLUS
DOCUMENT NUMBER: 113:91392
TITLE: Tetrahydroaminoacridine (tacrine) stimulates neurosecretion at mammalian motor endplates
AUTHOR(S): Thesleff, S.; Sellin, L. C.; Taagerud, S.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Lund, Lund, Swed.
SOURCE: British Journal of Pharmacology (1990), 100(3), 487-90
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tacrine (20 μM) induced, like 4-aminoquinoline (4-AQ, 200 μM), the appearance of a population of miniature endplate potentials (m.e.p.ps) with more than twice the normal amplitude or time-to-peak. The times-to-peak of nerve impulse-evoked endplate potentials were not similarly affected. Cholinesterase inhibition by edrophonium (25 μM) did not prevent tacrine or 4-AQ from inducing this population of m.e.p.ps. Nerve-muscle prepns. in which the normal calcium-sensitive quantal release of acetylcholine had been blocked by botulinum neurotoxin type A also responded to tacrine by an increase in the frequency of giant or slow m.e.p.ps. Reduction of the temperature from 30° to 14° reduced the frequency of giant or slow m.e.p.ps. induced either by tacrine or by 4-AQ. A similar effect was obtained by colchicine (5 mM). This supports the idea that proximo-distal axonal transport is required for the secretory activity. The neurosecretion evoked by tacrine could explain the therapeutic effects of the drug claimed in the treatment of Alzheimer's type of dementia.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(neuromuscular transmission stimulation by, Alzheimer's disease treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

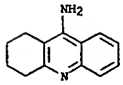


L11 ANSWER 183 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:471171 HCAPLUS
DOCUMENT NUMBER: 113:71171
TITLE: Therapeutic effect of THA on hemicholinium-3-induced learning impairment is independent of serotonergic and noradrenergic systems
AUTHOR(S): Hagan, J. J.; Jansen, J. H. M.; Nefkens, F. E. W.; De Boer, T.
CORPORATE SOURCE: Sci. Dev. Group, Organon Int. B.V., Oss, NL-5340 BH, Neth.
SOURCE: Psychopharmacology (Berlin, Germany) (1990), 101(3), 376-83
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine (THA: Tacrine) has previously been shown to reverse deficits in spatial discrimination learning induced by hemicholinium-3 (HC3). In the present expts., the effects of prior depletion of serotonin (5-HT) or noradrenaline (NA) on this reversal were examined In the first experiment, 5-HT lesions were made by injecting 5,7-DHT (2 + 50 μg/5 μL) into the lateral ventricles of rats pretreated with desmethylimipramine (DMI 25 mg/kg i.p.). A permanently indwelling guide tube was then implanted over the right lateral ventricle. Subsequent testing, under drug-free conditions, revealed no effect of the lesion on the number of trials needed to attain criterion (nine consecutive correct choices) in two-platform spatial discrimination learning in a watermaze. Using a latin square design rats were then tested for the effects of HC-3 and THA. HC-3 (5 μg/5 μL ICV) or placebo (CSF) were injected 60 min before the start of a 30-trial training session. THA (4.6, 10 mg/kg s.c.) or placebo were then injected 15 min before training. Choice accuracy but not choice latency was impaired by HC-3 and the effect was reversed by THA in both sham operated and 5-HT lesioned rats. In the second experiment, two injections of DSP-4 (50 mg/kg i.p.) were given, following cannulation, to deplete forebrain NA. The lesion had no effect on spatial learning under drug-free conditions and failed to block the THA-induced reversal of spatial discrimination learning deficits following HC-3. These results confirm that forebrain **acetylcholine** depletion by HC-3 impairs spatial discrimination learning and that the deficit is reversed by THA. However, concomitant depletion of forebrain 5-HT or NA does not block the ameliorative effect of THA.
IT **321-64-2**
RL: BIOL (Biological study)
(learning impairment from hemicholinium-3 reversal by, nervous system in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

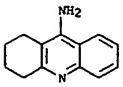


L11 ANSWER 183 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 184 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:434651 HCAPLUS
DOCUMENT NUMBER: 113:34651
TITLE: Low dose tetrahydroaminoacridine (THA) improves cognitive function but does not affect brain **acetylcholine** in rats
AUTHOR(S): Hodges, H.; Ribeiro, A. M.; Gray, J. A.; Marchbanks, R. M.
CORPORATE SOURCE: Dep. Psychol., Inst. Psychiatry, London, SE5 8AF, UK
SOURCE: Pharmacology, Biochemistry and Behavior (1990), 36(2), 291-8
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eight days of treatment with two low doses of tetrahydroaminoacridine (THA), given once daily, substantially improved radial maze performance in two groups of rats which showed persistent deficits either after ibotenic acid lesions at the source of forebrain cholinergic projections, or after 28 wk treatment with alc. (20% volume/volume) in drinking water. However, in immature, aged or aged and alc.-treated rats, **acetylcholine** content was not affected in any of the brain areas measured, even though the treatment regime had proved behaviorally effective. Inhibition of brain acetylcholinesterase activity was only marginally increased by this treatment regime. Thus, if THA influences behavior by enhancing cholinergic transmission, its effects do not appear to be related to its activity as a cholinesterase inhibitor, and alternative mechanisms of action should be investigated.
IT **321-64-2**, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(brain **acetylcholine** level lack of response to, in improvement of cognition)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 185 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:434643 HCAPLUS
DOCUMENT NUMBER: 113:34643
TITLE: Attenuation of serotonin-suppressed [3H] **acetylcholine** release by tetrahydroaminoacridine and dendrotoxin: interaction with minaprine binding site
AUTHOR(S): Muramatsu, Makoto; Chaki, Shigeyuki; Usuki-Ito, Chika; Otomo, Susumu
CORPORATE SOURCE: Res. Cent., Taisho Pharm. Co., Ltd., Saitama, 330, Japan
SOURCE: Research Communications in Chemical Pathology and Pharmacology (1990), 68(2), 131-42
CODEN: RCCPB8; ISSN: 0034-5164
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5-Hydroxytryptamine (5-HT) inhibited K+-induced [3H]**acetylcholine** ([3H]ACh) release from rat hippocampal slices dose-dependently. Minaprine [3-(2-morpholinoethylamino)-4-methyl-6-phenylpyridazine] and 9-amino-1,2,3,4-tetrahydroacridine (THA) attenuated the inhibition of [3H]ACh release by 5-HT. A neurotoxin isolated from the venom of Dendroaspis snake, dendrotoxin (DTX), also attenuated the 5-HT inhibited [3H]ACh release from hippocampal slices dose-dependently at doses of more than 3 + 10-7 g/mL (about 42 nM). Specific binding of [3H]minaprine to hippocampal membrane was dose-dependently inhibited by THA and DTX. The IC50 of THA and DTX for [3H]minaprine binding were about 32 and 0.7 μM, resp. Scatchard analyses showed that the inhibitory effects of THA and DTX were noncompetitive for [3H]ketanserin binding with IC50 of 28.8 and 26.2 μM, resp. These results suggest that THA and DTX attenuate the 5-HT-inhibited [3H]ACh release by blocking a voltage-dependent K+ current, and that they interact with the binding site of minaprine in the hippocampus.
IT **321-64-2**
RL: BIOL (Biological study)
(serotonin-inhibited **acetylcholine** release attenuation by, as potassium channel blocker, minaprine binding site interaction in, in hippocampus)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 186 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:400417 HCAPLUS
DOCUMENT NUMBER: 113:417
TITLE: Effect of the Nivalin-Pharmaneocarb combination on the digestive, respiratory, and cardiovascular systems of experimental animals
AUTHOR(S): Dimitrov, T.
CORPORATE SOURCE: Sofia, 1463, Bulg.
SOURCE: Doklady Bolgarskoi Akademii Nauk (1990), 43(1), 125-8
CODEN: DBANAD; ISSN: 0366-8681
DOCUMENT TYPE: Journal
LANGUAGE: English

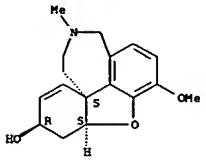
AB The effects of the Nivalin-Pharmaneocarb combination on the smooth muscles of the digestive system in vitro and on the bronchial muscles in vivo, as well as on the blood pressure and heart rate in exptl. animals were compared to those of Nivalin or Pharmaneocarb sep. The cholinomimetic effect of Nivalin on the spontaneous motor activity of small intestines and its potentiation of the action of acetylcholine remained unchanged in the Nivalin-Pharmaneocarb combination; the undesirable sympathomimetic effect of Pharmaneocarb on the cardiovascular system was eliminated. Blood pressure and heart rate were normalized, which reveals the complex interrelations between the cholinergic and catecholaminergic system in the regulation of blood pressure.

IT 1953-04-4, Nivalin
RL: BIOL (Biological study)
(cardiovascular and digestive and respiratory system response to)

RN 1953-04-4 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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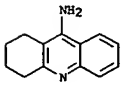
L11 ANSWER 187 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:191824 HCAPLUS
DOCUMENT NUMBER: 112:191824
TITLE: Behavioral effects after intrathecal administration of cholinergic receptor agonists in the rat
AUTHOR(S): Gillberg, P. G.; Hartvig, P.; Gordh, T.; Sottile, A.; Jansson, I.; Archer, T.; Post, C.
CORPORATE SOURCE: Hosp. Pharm., Univ. Hosp., Uppsala, S-751 85, Swed.
SOURCE: Psychopharmacology (Berlin, Germany) (1990), 100(4), 464-9
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The behavioral effects of nicotine and cytisine and the cholinesterase inhibitors of physostigmine and 9-amino-1,2,3,4-tetrahydroacridine (THA), administered intrathecally (IT) at the lumbar level in the rat, were evaluated. Antinociceptive dose relationships were established by the tail-immersion test. Total activity, locomotion, and rearing were also measured in computerized test boxes. The nicotinic receptor antagonist mecamylamine and the muscarinic receptor antagonist atropine were used to study the selectivity of the effects. Physostigmine and THA decreased total activity, locomotion, and rearing as compared to control. The motor effects of physostigmine were completely antagonized by atropine, whereas those of THA were antagonized only partly. Mecamylamine had no antagonist effect. Nicotine did not affect any activity parameter. Cytisine reduced total activity and locomotion 1-6 min after the dose. IT physostigmine, 15 μg, increased tail immersion latency for 30 min. No increase in response latency in this test was observed after the IT administration of nicotine or THA, whereas cytisine elicited a small increase. The IT administration of THA, nicotine, and cytisine was also associated with gnawing, vocalization, and hyperactivity and, in the case of THA, diarrhea. These effects were blocked by mecamylamine. Physostigmine-induced antinociception as well as the behavioral effects (including total activity, locomotion, and rearing) caused by physostigmine and by THA are most probably due to an action on spinal muscarinic receptors. Nicotinic receptors do not seem to be involved in spinal antinociception. Some aversive behavioral effects caused by the IT administration of nicotinic receptor agonists could, however, be attenuated by the spinal administration of the antagonist mecamylamine, which may indicate the involvement of nicotinic receptors in afferent sensory transmission.

IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(behavior response to)

RN 321-64-2 HCAPLUS

CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 187 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 188 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:112096 HCAPLUS
DOCUMENT NUMBER: 112:112096
TITLE: Preparation of galanthamine derivatives as cholinesterase inhibitors
PATENT ASSIGNEE(S): Stichting Biomedical Research and Advice Group, Neth.
SOURCE: Neth. Appl., 33 pp.
CODEN: NAXXAN
DOCUMENT TYPE: Patent
LANGUAGE: Dutch
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
NL 8800350	A	19890901	NL 1988-350	19880212
PRIORITY APPLN. INFO.:			NL 1988-350	19880212
OTHER SOURCE(S):	MARPAT 112:112096			

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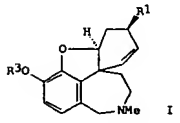


I

AB Galanthamine derivs. I (R1 = H, OH, O2CR2; R2 = C1-5 alkyl or hydroxyalkyl; R3 = H, Me) and the corresponding N-alkyl, N-alkenyl, and N-benzyl quaternized derivs. are prepared as peripheral cholinesterase inhibitors with little muscarinic activity on the heart and lungs. Thus, galanthamine was refluxed with allyl iodide in MeCN to provide N-allylgallanthamine-HI (II). Galananthamine-HBr in CH2Cl2 was treated with BBr3 under N to produce 6-O-dimethylgalanthamine (sanguinine). II or sanguinine-HI, each at 250 μg/kg i.v., caused 91 and 90% reversal, resp., of neuromuscular blockade with pancuronium bromide in rats.

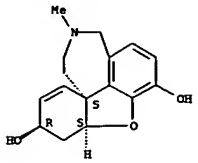
IT 60755-80-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as cholinergic agonist)

RN 60755-80-8 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepine-3,6-diol, 4a,5,9,10,11,12-hexahydro-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 188 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



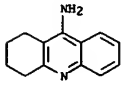
L11 ANSWER 189 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:69866 HCAPLUS
DOCUMENT NUMBER: 112:69866
TITLE: Correlation of brain levels of 9-amino-1,2,3,4-tetrahydroacridine (THA) with neurochemical and behavioral changes
AUTHOR(S): Nielsen, Jann A.; Mena, E. Edward; Williams, Ian H.; Nocerini, Mark R.; Liston, Dane
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, USA
SOURCE: European Journal of Pharmacology (1989), 173(1), 53-64
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB THA has been reported to cause improvement in patients with senile dementia of the Alzheimer type. The effects of THA were examined in vitro and in vivo to define its mechanism of action. In vitro, THA inhibits acetylcholinesterase (AChE) (IC50 = 223 nM) and blocks [3H]AFDX-116 (M2) and [3H]telenzepine (M1) muscarinic binding (IC50 1.5 and 9.1 μM resp.). In vivo levels of THA were 10-fold higher in brain than plasma following 3.2 mg/kg i.p., a dose which was active in reversing amnesia induced by scopolamine assessed in T-maze tests in rats and passive avoidance tests in mice. Addnl., these brain concns. were above the IC50 of THA for AChE inhibition. THA (5.6-17.8 mg/kg i.p.) also elevated acetylcholine levels in the rat central nervous system. THA-induced side effects were blocked by the central muscarinic antagonist scopolamine, but not by the peripheral antagonists methscopolamine and glycopyrrolate, nor by nicotinic antagonists. Thus, brain AChE inhibition by THA is sufficient to explain its purported therapeutic activity in Alzheimer's disease, and its favorable brain/plasma distribution in vivo may account for its central cholinergic action without inducing the severe peripheral cholinergic effects typically seen with other AChE inhibitors.

IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(scopolamine-induced amnesia treatment with, brain acetylcholine and acetylcholinesterase in relation to)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



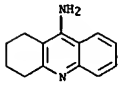
L11 ANSWER 190 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:48681 HCAPLUS
DOCUMENT NUMBER: 112:48681
TITLE: The mechanism of tetrahydroaminoacridine-evoked release of endogenous 5-hydroxytryptamine and dopamine from rat brain tissue prisms
AUTHOR(S): Robinson, T. N.; De Souza, R. J.; Cross, A. J.; Green, A. R.
CORPORATE SOURCE: Astra Neurosci. Res. Unit, London, WC1N 1PJ, UK
SOURCE: British Journal of Pharmacology (1989), 98(4), 1127-36
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Effects of tetrahydroaminoacridine (THA) on the release of endogenous 5-hydroxytryptamine (5-HT) from rat cortical prisms and dopamine from striatal prisms was studied. In the presence of K+ (1 mM), THA stimulated release of both 5-HT and dopamine. THA (100 μM)-evoked monoamine release was comparable, but not additive with the release produced by K+ (35 mM). The effect was not maximal at 1 mM THA. THA-evoked release of 5-HT was independent of the presence of Ca2+ in the external medium. Drugs acting on the cholinergic system, nicotine, mecamylamine, atropine, oxotremorine, physostigmine and neostigmine (all 10 μM) had no effect on 5-HT and dopamine release. 4-Aminopyridine (4-AP), a potent acetylcholine-releasing agent, had no effect on 5-HT release and was approx. 100 fold less active than THA on dopamine release. Both THA and reserpine enhanced the release of 5-HT in the presence of the monoamine oxidase inhibitor, pargyline. Reserpine- but not THA-evoked release was abolished in the absence of pargyline. Reserpine (5 mg/kg, i.p.) markedly depleted brain monoamine concns. 3 h after injection, while THA (15 mg/kg, i.p.) had no effect. Chloroamphetamine and fenfluramine both released 5-HT in a Ca2+-independent manner and with a similar potency to THA, while (+)-amphetamine released dopamine with a similar potency to THA. The effects of the amphetamines were not maximal at 1 mM. However, unlike THA, chloroamphetamine-evoked release of 5-HT was additive with release evoked by K+ (35 mM). Clomipramine (IC50 = 0.036 μM), imipramine (IC50 = 0.20 μM) and THA (IC50 = 19.9 μM) all inhibited the uptake of [3H]-5-HT into a P2 membrane preparation However, none of these compds. inhibited [3H]-5-HT uptake into tissue prisms during the release expts. in which the reuptake inhibitor fluoxetine (5 μM) was present. THA does not release endogenous 5-HT through a cholinergic, reserpine- or amphetamine-like mechanism or through inhibition of reuptake. The possibility exists that the release may occur via blockade of 4-AP-insensitive K+ channels.

IT 321-64-2
RL: BIOL (Biological study)
(dopamine and serotonin release from brain by, mechanism of)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 191 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:48617 HCAPLUS
DOCUMENT NUMBER: 112:48617
TITLE: Galanthamine, an acetylcholinesterase inhibitor: a time course of the effects on performance and neurochemical parameters in mice
AUTHOR(S): Sweeney, Joanne E.; Puttfarcken, Pamela S.; Coyle, Joseph T.
CORPORATE SOURCE: Dep. Environ. Health Sci., Johns Hopkins Sch. Med., Baltimore, MD, 21205, USA
SOURCE: Pharmacology, Biochemistry and Behavior (1989), 34(1), 129-37
CODEN: PBEHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

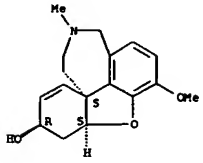
AB The time course of the effects of the long-acting acetylcholinesterase (AChE) inhibitor, galanthamine, on a spatial navigation task and on AChE and acetylcholine (ACh) levels were investigated in mice. Mice received either saline or ibotenic acid injections into the nucleus basalis magnocellularis (nBM). The control and nBM group were then trained to perform a modified Morris swim task and the time to find the hidden platform was recorded. The nBM group took longer time to find the platform than that by the control group in the reversal phase of testing. Galanthamine attenuated the performance deficit in the nBM-lesioned group in a time-dependent manner, with peak performance at 4 h after injection of 5.0 mg/kg galanthamine i.p. This dose impaired performance of the task in control mice, with the most severe deficits observed at 2 h after injections when motor activity was severely reduced. Galanthamine (5.0 mg/kg i.p.) decreased cortical AChE activity and increased cortical ACh content in control mice in a time-dependent manner. The time courses of the neurochem. effects, however, did not correlate precisely with the behavioral time course. Galanthamine concns. up to 1 + 10-5M did not affect choline acetyltransferase (ChAT) activity, [3H]hemicholinium-3 (HCh-3) binding to the choline carrier, [3H]quinuclidinylbenzilate (QNB) binding to muscarinic receptors, or [3H]acetylcholine binding to nicotinic receptors in cortical homogenates. AChE activity was inhibited by galanthamine in cortical homogenates with an IC50 of 4.1 + 10-7M. Galanthamine's ability to reverse cognitive deficits induced by nBM lesions, its relatively long half-life and its specificity of effects suggest that this drug may be effective in treating the central cholinergic deficits in Alzheimer's disease and related disorders.

IT 357-70-0, Galanthamine
RL: BIOL (Biological study)
(memory deficit response to, performance and neurochem. parameters in, acetylcholinesterase of brain in relation to)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 191 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



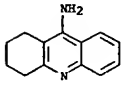
L11 ANSWER 192 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:15910 HCAPLUS
DOCUMENT NUMBER: 112:15910
TITLE: Quantitative whole-body autoradiographic determination of tacrine tissue distribution in rats following intravenous or oral dose
AUTHOR(S): McNally, William; Roth, Michelle; Young, Remedios; Bockbrader, Howard; Chang, Tsun
CORPORATE SOURCE: Parke-Davis Pharm. Res., Ann Arbor, MI, 48105, USA
SOURCE: Pharmaceutical Research (1989), 6(11), 924-30, 2 plates
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tacrine (1,2,3,4-tetrahydro-9-acridinamine) has been employed in diverse clin. situations but has recently been of considerable interest for the treatment of cognitive deficits associated with senile dementia (Alzheimer's disease). The present studies examined tissue distribution of radiolabeled tacrine by quant. whole-body autoradiog. Tacrine radioequivalents were widely distributed to tissue following i.v. or peroral dose, with an apparently prolonged absorption phase following the peroral dose. The presence of high levels of activity in kidneys and ureters indicates a major role for urinary excretion, but there is also evidence for biliary excretion and direct secretion of compound or metabolites into the intestinal lumen. Tacrine was rapidly taken up into the brain and demonstrated regional localization to cortex, hippocampus, thalamus, and striatum. Although the inhibition of acetylcholinesterase by tacrine is well documented, regional uptake in brain did not correlate consistently with distribution of the enzyme, supporting suggestions by others that the alleged action of tacrine in treatment of senile dementia may be by mechanisms other than cholinesterase inhibition.

IT 321-64-2, Tacrine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



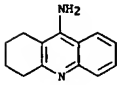
L11 ANSWER 193 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:15835 HCAPLUS
DOCUMENT NUMBER: 112:15835
TITLE: Alzheimer's disease and THA: a review of the cholinergic theory and of preliminary results
AUTHOR(S): Boller, F.; Forette, F.
CORPORATE SOURCE: Cent. Paul Broca, Paris, 75014, Fr.
SOURCE: Biomedicine & Pharmacotherapy (1989), 43(7), 487-91
CODEN: BIPHEX; ISSN: 0753-3322
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 33 refs. The cholinergic theory is based on the assumption that **acetylcholine** metabolism plays an important role in memory processes and that the deterioration of memory and other cognitive functions in Alzheimer's disease (AD) is directly related to degeneration of cerebral presynaptic cholinergic neurons. This article reviews various therapeutic strategies based on this theory and particularly that of using cholinesterase inhibitors such as tetrahydroaminoacridine (THA). The few available studies, all preliminary, on THA are reviewed. They show that THA is neither a cure nor a definitive treatment for AD. However, the preliminary reports suggest for the most part a certain degree of efficacy, greater at any rate than the efficacy of other pharmaceutical agents tried so far. Despite the apparent multiplicity of pharmacol. actions of THA, it appears that the cholinergic hypothesis remains valid and should be pursued further.

IT 321-64-2
RL: BIOL (Biological study)
(Alzheimer's disease treatment with, in humans)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



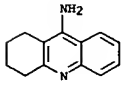
L11 ANSWER 194 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1990:523 HCAPLUS
DOCUMENT NUMBER: 112:523
TITLE: Cholinesterase inhibitor therapy for Alzheimer dementia: what do animal models tell us?
AUTHOR(S): Sherman, Kathleen A.; Messamore, Erik
CORPORATE SOURCE: Sch. Med., South. Illinois Univ., Springfield, IL, 62794, USA
SOURCE: Progress in Clinical and Biological Research (1989), 317(Alzheimer's Dis. Relat. Disord.), 1209-22
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An in vitro IC50 of ≤1 μM tacrine (THA) for brain or red cell acetylcholinesterase (AChE) was found, dependent on the substrate concentration
Results were independent of tissue dilution in vitro. After in vivo administration of THA to rats, the inhibition of plasma cholinesterase (ChE) or brain acetylcholinesterase (AChE) declined as a log function of tissue dilution The degree of inhibition is underestimated as a result of dilution of tissue for enzyme assay. Minimal tissue dilution was used to establish the dose-response and time-course functions after s.c. administration of THA and to compare the effect of THA in brain regions with that on blood enzymes. Pons-medulla AChE was less sensitive to the effects of THA than hippocampus, cortex, cerebellum, or plasma ChE, particularly at doses of ≥2.5 mg/kg. It is concluded that long-lasting inhibition of the metabolism of **acetylcholine** is the most plausible explanation to THA's pharmacol. activity.

IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**acetylcholine** metabolism inhibition by, Alzheimer's dementia treatment in relation to)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 195 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:639543 HCAPLUS
DOCUMENT NUMBER: 111:239543
TITLE: Nicotine agonists and antagonists as smoking deterrents
INVENTOR(S): Abood, Leo G.
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 5 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

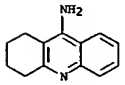
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4835162	A	19890530	US 1987-14018	19870212
US 4966916	A	19901030	US 1989-325746	19890320

PRIORITY APPLN. INFO.: US 1987-14018 A3 19870212

AB Tobacco smoking is inhibited by administering 3-300 mg total daily dose of a nicotine antagonist selected from 3-quinuclidinyl benzoate (I) or methylcarbamate (II) to the smoker. 3-Quinuclidinol (III) (0.05 mol) was treated with 0.05 mol BzCl in CH2Cl2 at room temperature to give 40% I; treatment of III with MeNCO gave II. I and II inhibited nicotine-induced prostration in rats with EC50 of 200 and 100 nmol, resp. The desire for tobacco is diminished by the oral administration of a tablet or capsule containing 25 mg I 3 times daily for 5-8 wk.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nicotine antagonist activity of)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

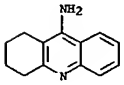


L11 ANSWER 196 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:625161 HCAPLUS
DOCUMENT NUMBER: 111:225161
TITLE: Multiple actions of THA on cholinergic neurotransmission in Alzheimer brains
AUTHOR(S): Nordberg, Agneta; Nilsson-Haakansson, Lena; Adem, Abdu; Lai, Zhennan; Winblad, Bengt
CORPORATE SOURCE: Dep. Pharmacol., Uppsala Univ., Uppsala, Swed.
SOURCE: Progress in Clinical and Biological Research (1989), 317(Alzheimer's Dis. Relat. Disord.), 1169-78
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of 1,2,3,4-tetrahydro-9-aminoacridine (THA) on acetylcholine release from human brain slices were studied. The release from normal brain cortical tissue was decreased by THA probably due to a neg. feedback mediated by presynaptic muscarinic autoreceptors. Brain cortex from patients with Alzheimer disease and senile dementia of Alzheimer type released acetylcholine at control levels in response to THA. This effect was inhibited by muscarinic and nicotinic antagonists (atropine, mecamylamine, dihydro-β-erythroidine). Subchronic treatment of rats with 10 mg THA/kg s.c. twice daily increased the number of high-affinity nicotinic receptors in the brain cortex but similar treatment with physostigmine had no such effect. The nos. of muscarinic receptors decreased in response to both THA and physostigmine.

IT 321-64-2, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: BIOL (Biological study)
(brain release of acetylcholine response to, in Alzheimer disease and senile dementia in human, muscarinic and nicotinic receptors in relation to)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

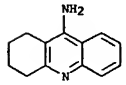


L11 ANSWER 197 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:567322 HCAPLUS
DOCUMENT NUMBER: 111:167322
TITLE: Carbachol inhibits atrial contractility in the presence of potassium channel blocking agents
AUTHOR(S): Groschner, K.; Kukovetz, W. R.
CORPORATE SOURCE: Inst. Pharmakodyn. Toxikol., Karl-Franzens-Univ., Graz, A-8010, Austria
SOURCE: Journal of Cardiovascular Pharmacology (1989), 14(4), 648-52
CODEN: JCPCDT; ISSN: 0160-2446
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To elucidate the role of K+ channel activation in muscarinic inhibition of atrial contractility, the authors studied the influence of K+ channel blockers on the effects of the muscarinic agonist carbachol in isolated guinea pig auricles. BaCl2, tetraethylammoniumchloride (TEA), and 9-aminotetrahydroacridine (THA), which block K+ channels, were tested for their ability to antagonize the effects of carbachol on atrial contractility and functional refractory period. Due to inhibition of K+ outward currents, BaCl2, TEA, and THA markedly blocked the carbachol-induced shortening of refractory period and, to a lesser extent, antagonized its neg. inotropic action. BaCl2, TEA, and THA shifted the concentration-response curve of the neg. inotropic action of carbachol to the right; the most pronounced effect was obtained with TEA. The maximum neg. inotropic effect of carbachol, however, was only slightly reduced by the K+ channel blockers, and carbachol clearly inhibited atrial contractility even in the absence of any shortening of refractory period. These results suggest the existence of an addnl. cholinergic, neg. inotropic mechanism, distinctly different from activation of atrial K+ channels.

IT 321-64-2
RL: BIOL (Biological study)
(atrial contraction inhibition by carbachol in presence of)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

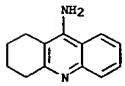


L11 ANSWER 198 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:567212 HCAPLUS
DOCUMENT NUMBER: 111:167212
TITLE: The cholinergic pharmacology of tetrahydroaminoacridine in vivo and in vitro
AUTHOR(S): Hunter, A. J.; Murray, T. K.; Jones, J. A.; Cross, A. J.; Green, A. R.
CORPORATE SOURCE: Astra Neurosci. Res. Unit, London, WC1N 1PJ, UK
SOURCE: British Journal of Pharmacology (1989), 98(1), 79-86
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of tetrahydroaminoacridine (THA) on cholinergically mediated behavior in the rat and mouse was investigated. In addition, the actions of this compound on cholinesterase activity and on muscarinic and nicotinic receptors was also examined Administration of THA (5-20 mg/kg, i.p.) produced a dose-dependent increase in tremor, hypothermia, and salivation in both rats and mice. A similar profile of activity was seen following physostigmine (0.1-0.6 mg/kg) administration. THA was .apprx.50-fold less potent than physostigmine in inducing behavioral change but its effects persisted for over twice as long as those of physostigmine. For example THA-induced hypothermia was still present at 4 h in the mouse and 8 h in the rat. In vitro, THA was a potent noncompetitive inhibitor of rat brain cholinesterase (IC50: 57 nM) and bovine erythrocyte acetylcholinesterase (IC50: 50 nM) but was a more potent inhibitor of horse serum butyryl cholinesterase (IC50: 7.2 nM). Radioligand binding studies indicated that THA binds nonselectively but with moderate potency to both M1 (Ki: 600 nM) and M2 (Ki: 880 nM) muscarinic receptors. THA also interacted with the allosteric site present on cardiac M2 receptors. Thus, THA is a reversible noncompetitive inhibitor of cholinesterase with a long half-life (compared with physostigmine). It also may antagonize muscarinic receptors at high doses. The long half-life may account for its reported efficacy in the treatment of Alzheimer's disease.

IT 321-64-2
RL: BIOL (Biological study)
(cholinesterase inhibition and muscarinic antagonism by)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



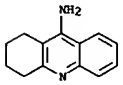
L11 ANSWER 199 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1989:526955 HCAPLUS
DOCUMENT NUMBER: 111:126955
TITLE: Multiple in vitro interactions with and differential in vivo regulation of muscarinic receptor subtypes by tetrahydroaminoacridine
AUTHOR(S): Flynn, Donna D.; Mash, Deborah C.
CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, 33136, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1989), 250(2), 573-81
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tetrahydroaminoacridine (THA) is known to be a potent centrally acting cholinesterase inhibitor. In this report, the effects of THA in vivo and in vitro on the binding of muscarinic agonists and antagonists to putative M1 and M2 receptor subtypes were assessed in rat brain membranes. THA competitively inhibited labeled agonist and antagonist binding to membranes prepared from M1 and M2 enriched brain regions. The dissociation of radiolabeled antagonists from muscarinic receptors was decelerated markedly by THA. The half-time for dissociation of [3H]oxotremorine-M from the high affinity state of M1 and M2 receptors was unaffected by THA. Chronic THA administration resulted in a selective down regulation in the number of M1 receptors assayed directly with the M1-selective antagonist, [3H]pirenzepine. The decrease in the binding capacity of [3H]pirenzepine was correlated pos. with the duration of drug treatment. Saturation anal. of [3H]pirenzepine binding confirmed that this loss in binding capacity was due to a reduction in the number of binding sites and not an altered affinity of the receptor for [3H]pirenzepine. Carbachol-[3H]pirenzepine competition revealed no change in the ratio of high and low affinity agonist states of the M1 receptor with chronic THA administration. In vitro studies demonstrate further than the total number of muscarinic receptors was decreased significantly, whereas putative M2 receptors, measured directly with the agonist [3H]oxotremorine-M or estimated by pirenzepine-[3H]quinuclidinyl benzilate competition, were unchanged. Thus, THA exhibits multiple actions at primary and secondary recognition sites on putative M1 and M2 subclasses of muscarinic receptors. The results suggest further that the clin. pharmacol. of THA may represent a composite efficacy of THA at multiple sites on cholinergic synapses.

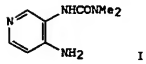
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(cholinergic neurotransmission response to, muscarinic receptor interaction in)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 200 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1989:490251 HCAPLUS
DOCUMENT NUMBER: 111:90251
TITLE: Effects of LF-14, THA and physostigmine in rat hippocampus and cerebral cortex
AUTHOR(S): Potter, P. E.; Nitta, S.; Chaudhry, I.; Lalezari, I.; Goldiner, P.; Foldes, F. F.
CORPORATE SOURCE: Dep. Anesthesiol., Albert Einstein Coll. Med., Bronx, NY, 10467, USA
SOURCE: Neurochemistry International (1989), 14(4), 433-8
CODEN: NEUIDS; ISSN: 0197-0186
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

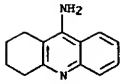
AB The effects of physostigmine, tetrahydroaminoacridine (THA), and LF-14 [3,3-dimethyl-1(4-amino-3-pyridyl)urea] (I), a 3,4-diaminopyridine derivative, were compared on inhibition of acetylcholinesterase (AChE) activity and release of [3H]acetylcholine (ACh) from rat brain cortical and hippocampal slices. All 3 compds. caused a concentration dependent inhibition of AChE, with an order of potency physostigmine > THA > LF-14. The elec. stimulated release of ACh from hippocampal and cortical slices was decreased by 10-5M physostigmine, although the effect was significant only in cortex. THA (5 + 10-5M) caused a slight, but nonsignificant decrease in ACh release from both tissues. In contrast, LF-14 (5 x 10-5M) caused an .apprx.3-fold enhancement of stimulated release. When AChE was inhibited by prior addition of physostigmine, THA caused only a slight enhancement of ACh release, whereas LF-14 greatly increased release. ACh release was also reduced by stimulation of presynaptic muscarinic receptors with oxotremorine. In this case, THA had no effect on ACh release, while LF-14 was able to reverse the inhibition. Thus, LF-14 acts to promote ACh release through blocking K+ channels, and has a less potent AChE inhibitory effect. It is possible that a compound like LF-14 could be useful in treating diseases of cholinergic dysfunction such as Alzheimer's disease, by both promoting the release of ACh and inhibiting its breakdown.

IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cholinergic neurotransmission in brain response to)

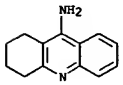
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 199 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 200 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

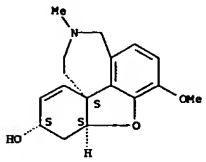


L11 ANSWER 201 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:490232 HCAPLUS
DOCUMENT NUMBER: 111:90232
TITLE: Hemicholinium-3 impairs spatial learning and the deficit is reversed by cholinomimetics
AUTHOR(S): Hagan, J. J.; Jansen, J. H. M.; Broekkamp, C. L. E.
CORPORATE SOURCE: Sci. Dev. Group, Organon Int. B.V., Oss, 5340 BH, Neth.
SOURCE: Psychopharmacology (Berlin, Germany) (1989), 98(3), 347-56
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of hemicholinium-3 (HC-3) on spatial discrimination learning were studied. The results showed that spatial learning was dose dependently impaired by HC-3, choice accuracy being reduced to chance levels by the higher dose. There was no evidence of motoric difficulty, as choice latencies were not significantly increased. Expts. were then conducted to test for reversal of the deficit using a range of psychotropic drugs. Rats were treated with artificial cerebrospinal fluid (CSF) or HC-3 (5 μg/rat intracerebroventricularly) 60 min prior to testing and test drugs were injected 15 min before testing. Some doses of physostigmine (46-460 μg/kg/s.c.) and tetrahydroaminoacridine (THA) (2.2-10 mg/kg/s.c.) reversed the spatial learning deficit. The muscarinic agonists arecoline (0.046-1 mg/kg/s.c.), aceclidine (1-10 mg/kg/s.c.), oxotremorine (30-100 μg/kg/s.c.) and RS-86 (0.46, 1.0 μg/kg/s.c.) were also effective. Pilocarpine (0.22-2.2 mg/kg/s.c.) showed marginal activity and isoarecoline (4.6-10 mg/kg/s.c.) was inactive. Nicotine (0.32, 1, 3.2 mg/kg/s.c.) and piracetam (10, 30, 100 mg/kg i.p.) were also inactive. The α2 agonist, clonidine (46, 100 μg/kg s.c.) and the antagonist idazoxan (32, 100 μg/kg s.c.) were also inactive. Learning deficits were not reversed by haloperidol (20, 60 μg/kg), amphetamine (0.1, 0.46 mg/kg), the selective 5-HT1A agonist 8-OH-DPAT (30, 100 μg/kg) or by the benzodiazapine antagonist ZK 93426 (1, 3.2, 10 mg/kg). The results show that forebrain Ach depletion by HC-3 impairs spatial discrimination learning and these deficits are reversed by cholinesterase inhibitors and some muscarinic receptor agonists. Some degree of pharmacol. selectivity is indicated by the failure of a range of other drugs to reverse the impairments.
IT 321-64-2
RL: BIOL (Biological study)
(hemicholinium spatial learning deficit response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

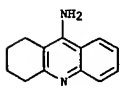


L11 ANSWER 202 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:470283 HCAPLUS
DOCUMENT NUMBER: 111:70283
TITLE: Pharmacokinetics of galanthamine hydrobromide after single subcutaneous and oral dosage in humans
AUTHOR(S): Mihailova, D.; Yamboliev, I.; Zhivkova, Z.; Tencheva, J.; Jovovich, V.
CORPORATE SOURCE: Sci. Inst. Pharm. Pharmacol., Sofia, Bulg.
SOURCE: Pharmacology (1989), 39(1), 50-8
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Galanthamine hydrobromide (Nivalin) (10 mg) was given s.c. and orally to volunteers. Galanthamine and its metabolites were quantified in plasma and urine by reversed-phase HPLC. An unusual 2-stage absorption and biexponential drug decline were observed Galanthamine plasma peaks (1.24 μg/mL after s.c. and 1.15 μg/mL after oral doses) were reached 2 h following administration, the t1/2(β) values being 5.70 and 5.26 h, resp. Minor epigalanthamine and galanthaminone plasma levels were detected. An almost complete urinary recovery of galanthamine and its metabolites was obtained within 72 h. The plasma AUC, Cmax, tmax and ka suggest that the s.c. and oral Nivalin formulations are bioequivalent.
IT 1668-85-5, Epigalanthamine
RL: BIOL (Biological study)
(as galanthamine metabolite, in humans)
RN 1668-85-5 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6S,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 203 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:433499 HCAPLUS
DOCUMENT NUMBER: 111:33499
TITLE: Tetrahydroaminoacridine and other allosteric antagonists of hippocampal M1 muscarine receptors
AUTHOR(S): Potter, Lincoln T.; Ferrendelli, Cynthia A.; Hanchett, Helene E.; Hollifield, Michael A.; Lorenzi, Matthew V.
CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, 33133, USA
SOURCE: Molecular Pharmacology (1989), 35(5), 652-60
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine (THA) and a variety of other nonclassical antagonists of muscarine receptors were studied for their ability to bind to primary and allosteric sites on muscarine receptors in rabbit hippocampal membranes. Competition curves between 13 antagonists and 1 nM [3H]pirenzepine (Kd = 3 nM) were simple mass action curves, but THA produced steeper curves, indicating pos. cooperativity. Nonetheless, THA inhibited the binding of low concns. of [3H]pirenzepine, [3H]N-methylscopalamine, and [3H]oxotremorine-M to M1 receptors with similar IC50 values, indicating competition for primary sites. Antagonists were also compared for their ability to bind to allosteric sites and to slow the dissociation of [3H]pirenzepine from primary sites. THA was 6-8-fold more potent than verapamil, d-tubocurare, quinidine, and secoverine, the next most effective allosteric agents, and THA was more effective. McN-A-343, allamine, pancuronium, and pirenzepine showed weaker allosteric effects. The large size and considerable rigidity of these compds. suggest large allosteric sites. The Hill coefficient for the allosteric effects of THA was 1.7, indicating more than 1 allosteric site. Solubilization of receptors did not alter steep inhibition curves between THA and [3H]quinuclidinyl benzilate or THA-induced slowing of the dissociation of this ligand. Hence, cooperative allosteric effects of THA are probably exerted on receptor monomers. Inhibition curves between THA and [3H]oxotremorine-M were not steep, and THA had no (allosteric) effect on the dissociation of this ligand from M1 or M2 receptors. Thus, the high affinity agonist conformation of muscarine receptors, once formed, may not bind THA readily. The present results indicate that compds. that can act allosterically may compete with acetylcholine for primary receptor sites but that allosteric effects of these drugs on muscarine receptors are not likely to be important clin.
IT 321-64-2
RL: BIOL (Biological study)
(M1 muscarinic receptor antagonist activity of, in brain hippocampus, allosteric effects in)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

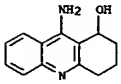


L11 ANSWER 204 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:185780 HCAPLUS
DOCUMENT NUMBER: 110:185780
TITLE: Physostigmine, tacrine and metrifonate: the effect of multiple doses on acetylcholine metabolism in rat brain
AUTHOR(S): Hallak, M.; Giacobini, E.
CORPORATE SOURCE: Sch. Med., South. Illinois Univ., Springfield, IL, 62794-9230, USA
SOURCE: Neuropharmacology (1989), 28(3), 199-206
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of 2 consecutive i.m. doses of 3 cholinesterase inhibitors (physostigmine, tetrahydroaminoacridine and metrifonate) were compared in rats. The results revealed major differences in biochem. effects on the brain of the rat including the extent and duration of inhibition of cholinesterase, inhibition of release of acetylcholine and increase in levels of acetylcholine. Side effects were also markedly different in the time of appearance, duration and severity. These results suggest that there are significant differences in the mechanisms of action of various cholinesterase inhibitors. Since all 3 cholinesterase inhibitors are currently used in the exptl. treatment of Alzheimer's disease, these findings have potential implications for the symptomatic therapy of these patients.
IT 321-64-2, Tacrine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(acetylcholine metabolism by brain response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 205 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:166665 HCAPLUS
DOCUMENT NUMBER: 110:166665
TITLE: Effect of scopolamine and HP 029, a cholinesterase inhibitor, on long-term potentiation in hippocampal slices of the guinea pig
AUTHOR(S): Tanaka, Yoshitaka; Sakurai, Masao; Hayashi, Shoryo
CORPORATE SOURCE: Lab. Pharmacol., Hoechst Japan Ltd., Saitama, 350, Japan
SOURCE: Neuroscience Letters (1989), 98(2), 179-83
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of scopolamine (a muscarinic antagonist and a cholinesterase inhibitor on long-term potentiation (LTP) of population spikes was studied in a guinea pig hippocampal slice preparation After brief application of each drug (10 min), LTP in CA1 and CA3 was induced by tetanic stimulation delivered to the commissural/association fibers and mossy fibers, resp. Scopolamine at 10 μM had no effect on LTP in CA1 but suppressed LTP in CA3. The cholinesterase inhibitor 9-amino-1,2,3,4-tetrahydroacridine-1-ol maleate (HP 029) at 10 μM enhanced LTP both in CA1 and CA3. These results suggest that the cholinergic system is involved in producing LTP in CA3. Another possible mechanism of the effect of HP 029 on LTP in CA1 is discussed.
IT 118909-22-1, HP 029
RL: BIOL (Biological study)
(brain hippocampal long-term potentiation response to)
RN 118909-22-1 HCAPLUS
CN 1-Acridinol, 9-amino-1,2,3,4-tetrahydro-, (2Z)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 124027-47-0
CMF C13 H14 N2 O

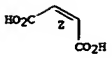


CM 2

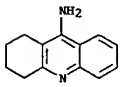
CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.

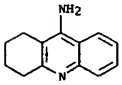
L11 ANSWER 205 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



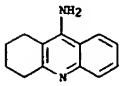
L11 ANSWER 206 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:166115 HCAPLUS
DOCUMENT NUMBER: 110:166115
TITLE: Effects of cholinergic drugs on learning impairment in ventral globus pallidus-lesioned rats
AUTHOR(S): Ueki, Akinori; Miyoshi, Koho
CORPORATE SOURCE: Dep. Neuropsychiatry, Hyogo Coll. Med., Hyogo, Japan
SOURCE: Journal of the Neurological Sciences (1989), 90(1), 1-21
CODEN: JNSCAG; ISSN: 0022-510X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The excitotoxin kainic acid (10 nmol/μL) was used to produce bilateral lesions in the nucleus basalis magnocellularis (NBM) of rats, which provides extensive cholinergic innervation to the cerebral cortex. The behavioral effects of physostigmine, THA (9-amino-1,2,3,4-tetrahydroacridine hydrochloride), and NIK-247 were investigated by observing locomotor activity, shock sensitivity, and passive avoidance response in the NBM-lesioned rats. The lesions caused no sensorimotor disturbances. Oral administration of 1 and 2 mg physostigmine/kg reduced the locomotor activity in the NBM-lesioned rats, while physostigmine (0.5 mg/kg), THA (1 or 3 mg/kg) and NIK-247 (1 or 3 mg/kg) had no effect. Compared with the sham-operated controls, the NBM-lesioned rats exhibited deficits in the retention of passive avoidance responses. THA (1 or 3 mg/kg) and NIK-247 (1 or 3 mg/kg) elicited good retention of the passive avoidance responses. Rats with NBM lesions showed impaired acquisition of passive avoidance responses when trained repeatedly at 24-h intervals. When post-training NBM lesions were induced, there was a rapid extinction of the acquired passive avoidance responses. THA or NIK-247 administered at 3 mg/kg increased the response latencies of post-trained NBM-lesioned rats. THA or NIK-247 administered orally once a day in doses of 1 or 3 mg/kg increased acetylcholine in the cerebral cortex of NBM-lesioned rats after the 21st administration. THA and NIK-247 may exert an ameliorating effect on memory disturbed by NBM lesions in rats.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(learning and memory improvement by, Alzheimer disease in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



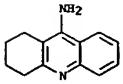
L11 ANSWER 207 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:166049 HCAPLUS
DOCUMENT NUMBER: 110:166049
TITLE: Tetrahydroaminoacridine but not 4-aminopyridine inhibits high-affinity choline uptake in striatal and hippocampal synaptosomes
AUTHOR(S): Buyukuysal, R. Levent; Wurtman, Richard J.
CORPORATE SOURCE: Dep. Brain Cognit. Sci., Massachusetts Inst. Technol., Cambridge, MA, 02139, USA
SOURCE: Brain Research (1989), 482(2), 371-5
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tetrahydroaminoacridine (THA), 4-aminopyridine (4-AP), and tetraethylammonium (TEA) on high-affinity choline uptake and the release of newly synthesized acetylcholine (ACh) from striatal and hippocampal synaptosomes and on choline acetyltransferase (ChAT) activity in rat striatal synaptosomes were studied. Incubation of the striatal synaptosomes with THA (5-100 μM) caused a concentration-dependent inhibition in the accumulation of soluble 14C-labeled compds. ([14C]choline and [14C]ACh); at concns. of <50 μM THA also completely suppressed the release of newly synthesized [14C]ACh. 4-AP slightly decreased the accumulation of [14C]ACh in the striatal synaptosomes without affecting that of [14C]choline, but markedly increased the release of [14C]ACh into the medium; hence the drug stimulated net choline uptake (by 19, 20, and 31%, resp., in the presence of 5, 50, and 100 μM THA). Like THA, but not 4-AP, TEA decreased both the accumulation of 14C-compds. in the striatal synaptosomes and the release of newly synthesized [14C]ACh. Similar effects of THA and 4-AP on high-affinity choline uptake and the release of [14C]ACh were also observed when hippocampal synaptosomes were used. THA and 4-AP are structurally similar and share with TEA the ability to block certain potassium channels. In spite of these similarities, the compds. produced opposite effects on net choline uptake by striatal and hippocampal synaptosomes. The results are discussed in terms of Alzheimer's disease therapy.
IT 321-64-2
RL: BIOL (Biological study)
(choline uptake by brain synaptosome response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



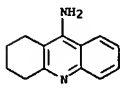
L11 ANSWER 208 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:165949 HCAPLUS
DOCUMENT NUMBER: 110:165949
TITLE: Effects of cholinergic and adrenergic enhancing drugs on memory in aged monkeys
AUTHOR(S): Bartus, Raymond T.; Dean, Reginald L., III
CORPORATE SOURCE: Lederle Lab., Pearl River, NY, USA
SOURCE: Curr. Res. Alzheimer Ther.: Cholinesterase Inhib. (1988), 179-90. Editor(s): Giacobini, Ezio; Becker, Robert E. Taylor & Francis: New York, N. Y. CODEN: 56LFA7
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The effects of tetrahydroaminoacridine, 3,4-diaminopyridine, and physostigmine on mental performance were studied in memory-impaired aged Cebus monkeys. Physostigmine effects were the most visible and reliable in comparison with the other 2 agents. An addnl. study with acute or subchronic treatment with clonidine alone or in combination with the muscarinic agonists arecoline and oxotremorine did not show any consistent memory improvement. Possible relations to Alzheimer disease are discussed.
IT 321-64-2
RL: BIOL (Biological study)
(memory performance response to, in aged monkeys, Alzheimer disease in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 209 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:147632 HCAPLUS
DOCUMENT NUMBER: 110:147632
TITLE: Actions of THA, 3,4-diaminopyridine, physostigmine, and galanthamine on neuronal potassium(+) currents at a cholinergic nerve terminal
AUTHOR(S): Harvey, Alan L.; Rowan, Edward G.
CORPORATE SOURCE: Dep. Physiol. Pharmacol., Univ. Strathclyde, Glasgow, G1 1XW, UK
SOURCE: Curr. Res. Alzheimer Ther.: Cholinesterase Inhib. (1988), 191-7. Editor(s): Giacobini, Ezio; Becker, Robert E. Taylor & Francis: New York, N. Y. CODEN: 56LFA7
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The effects of tetrahydroaminoacridine (THA), 3,4-diamnopyridine, physostigmine and galanthamine or presynaptic action potentials and acetylcholinesterase activity were studied on the mouse neuromuscular junction as a model system for testing drugs for the treatment of Alzheimer's disease. All 4 drugs enhanced the cholinergic transmission. Diaminopyridine facilitated acetylcholine release by blocking presynaptic K+ channels but had no anticholinesterase activity. THA and physostigmine acted mainly via their anticholinesterase effects. Galanthamine had no detectable effects on the presynaptic action potentials.
IT 321-64-2
RL: BIOL (Biological study)
(cholinergic transmission response to, at neuromuscular junction as model, Alzheimer's disease in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

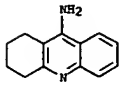


L11 ANSWER 210 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:147629 HCAPLUS
DOCUMENT NUMBER: 110:147629
TITLE: Accumulation and turnover of acetylcholine after administration of acetylcholinesterase inhibitors in rat brain
AUTHOR(S): Enz, Albert
CORPORATE SOURCE: SANDOZ Ltd., Basel, CH-4002, Switz.
SOURCE: Curr. Res. Alzheimer Ther.: Cholinesterase Inhib. (1988), 43-51. Editor(s): Giacobini, Ezio; Becker, Robert E. Taylor & Francis: New York, N. Y. CODEN: 56LFA7
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Acetylcholinesterase (AChE) inhibitors were added in vitro to enzyme prepns. from various rat brain regions. Physostigmine was .apprx.100 times more potent than RA7, which in turn was 3-4 times more potent than tacrine. No regional differences were found with either inhibitor. The pseudoirreversible mechanism common to RA7 and physostigmine enabled ex vivo measurement of the inhibitory effects of these drugs after oral or s.c. administration. Physostigmine, following s.c. administration, inhibited the enzyme in all brain regions with the same potency. However, RA7, in contrast to physostigmine, displayed a regional selectivity by preferentially inhibiting ex vivo AChE extracted from the cortex and hippocampus. The rank order of inhibition was cortex > hippocampus > striatum = pons/medulla. No inhibitors tested had any effects on acetylcholine levels and turnover in the pons/medulla region, in spite of the fact that they inhibited AChE activity measured ex vivo.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholine metabolism by brain response to and acetylcholinesterase inhibition by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

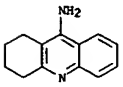


L11 ANSWER 211 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:128493 HCAPLUS
DOCUMENT NUMBER: 110:128493
TITLE: Effects of cholinergic drugs used in Alzheimer therapy at the mammalian neuromuscular junction
AUTHOR(S): Bradley, Ronald J.; Edge, Mark T.; Moran, Stephan G.; Freeman, Arthur M.
CORPORATE SOURCE: Sch. Med., Univ. Alabama, Birmingham, AL, USA
SOURCE: Curr. Res. Alzheimer Ther.: Cholinesterase Inhib. (1988), 199-209. Editor(s): Giacobini, Ezio; Becker, Robert E. Taylor & Francis: New York, N. Y. CODEN: 56LFA7
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The drugs which are used in Alzheimer therapy were tested at the rat neuromuscular junction. These drugs are known to inhibit acetylcholinesterase (AChE) in the case of 9-amino-1,2,3,4-tetrahydroacridine (THA), its close derivative HP 029, and physostigmine. On the other hand, 4-aminopyridine may increase acetylcholine (ACh) release by blocking presynaptic K+ channels. When transmission was blocked by reducing the release of ACh or by treatment with curare, THA could reverse the block at concns. which are well within the range found in the sera of AD patients treated with THA (<287 nM). The THA derivative HP 029 was less potent than THA but, at higher concns., it was as effective as THA in reversing block. The concentration of physostigmine required to reverse the block was higher than the maximum concentration which is found in serum after a single 2-mg oral dose. For the above 3 drugs a 10-fold higher concentration was required in order to block normal neuromuscular transmission.
In the case of 4-aminopyridine, the concentration required to reverse block was also higher than has been reported in human sera. However, the effects of 4-aminopyridine are complex and may involve ACh receptor (AChR)-channel block as well as AChE inhibition. It is possible that the reversal of curare-induced fade reported for 4-aminopyridine may involve AChE inhibition as well as K+-channel block. The low concns. of THA, HP 029, or physostigmine, which reversed transmission block, did not affect the shape of the compound nerve action potential or the compound muscle action potential. It is therefore likely that low concns. of these drugs do not affect K+ channels but rather inhibit the AChE at the synapse so that addnl. ACh is available to increase depolarization. The small increase in ACh concentration reaching the AChRs after treatment with therapeutic concns. of THA is not sufficient to interfere with normal synaptic transmission. The most parsimonious theory of THA action in AD is that it inhibits AChE in the brain and thereby raises the probability of synaptic transmission. This concept is supported by the finding that clin. concns. of THA reverse curare-induced block at the neuromuscular junction. The other drugs tested were not as effective as THA in reversing cholinergic block at therapeutic concns. The agonists choline or carbachol do not reverse curare-induced block but intensify this block. Therefore, the concept of AD therapy with agonists is not supported by studies at the mammalian neuromuscular junction.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(neuromuscular transmission response to, Alzheimer's disease therapy in relation to)
RN 321-64-2 HCAPLUS

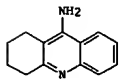
L11 ANSWER 211 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 212 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:108137 HCAPLUS
DOCUMENT NUMBER: 110:108137
TITLE: The relative potencies of cholinomimetics and muscarinic antagonists on the rat iris in vivo: effects of pH on potency of pirenzepine and telenzepine
AUTHOR(S): Hagan, J. J.; Van der Heijden, B.; Broekkamp, C. L. E.
CORPORATE SOURCE: CNS Pharmacol. Lab., Organon Int. B. V., Oss, 5340 BH, Neth.
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1988), 338(5), 476-83
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Topical administration of drugs to the cornea of anesthetized rats pretreated with clonidine provides a rapid and simple method for the detection of cholinomimetic activity, whether this is due to direct agonist activity, acetylcholinesterase inhibition or facilitation of transmitter release. In non-clonidine-treated rats antagonist effects are readily detected and both agonist and antagonist data tentatively suggest that contraction of the iris sphincter may be mediated through an M2 (ileal) receptor. Finally, the potency of pirenzepine and telenzepine were found to vary as a function of pH, an effect which appears to be mediated by facilitation of trans-corneal transport or diffusion and which may have important implications for understanding the mode of action of these drugs in anti-ulcer therapy.
IT 321-64-2
RL: BIOL (Biological study)
(miosis from)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

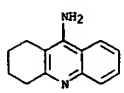


L11 ANSWER 213 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:583407 HCAPLUS
DOCUMENT NUMBER: 109:183407
TITLE: Blockade of a cardiac potassium channel by tacrine: interactions with muscarinic and adenosine receptors
AUTHOR(S): Freeman, Shirley Estelle; Lau, Wai Man; Szilagyi, Maria
CORPORATE SOURCE: Mater. Res. Lab., Def. Sci. Technol. Organ., Melbourne, 3032, Australia
SOURCE: European Journal of Pharmacology (1988), 154(1), 59-65
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

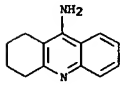


I

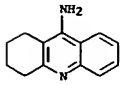
AB The centrally acting anticholinesterase drug tacrine (I) was shown to block K+ channels in guinea pig left atrium. It competitively blocks the neg. inotropic effects of adenosine, 2-chloroadenosine, and carbachol. Ka Values obtained from dose ratio plots were 2.5, 3.5 and 2.9 μM, resp. It was also able to antagonize the shortening of the action potential due to these compds. Doses of tacrine ranging from 1 to 4 μM restored the action potential configuration close to control values. Tacrine also antagonized the binding of [3H]QNB to membranes derived from the atrium and cerebral cortex. Xi Values of 1.0 and 1.3 μM were obtained, resp. Tacrine was a weak competitor of [3H]phenylisopropyladenosine binding in brain membranes. Its diverse pharmacol. effects may be relevant to its use in Alzheimer's disease.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(potassium channel blockade by, in heart, adenosine and muscarinic receptors in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



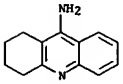
L11 ANSWER 214 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:563445 HCAPLUS
DOCUMENT NUMBER: 109:163445
TITLE: Tetrahydroaminoacridine selectively attenuates NMDA receptor-mediated neurotoxicity
AUTHOR(S): Davenport, Cynthia J.; Monyer, Hannelore; Choi, Dennis W.
CORPORATE SOURCE: Med. Cent., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: European Journal of Pharmacology (1988), 154(1), 73-8
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Addition of the acetylcholinesterase inhibitor 1,2,3,4-tetrahydro-9-aminoacridine (THA) at 1-3 mM markedly reduced the neuronal cell loss that otherwise followed brief exposure of murine cortical cell cultures to 500 μM N-methyl-D-aspartate (NMDA). This novel antagonism was selective for NMDA receptor-mediated toxicity, as it extended to glutamate toxicity but not to quisqualate toxicity, and was THA concentration-dependent between 100
μM and 3 mM, with the IC50 of approx. 500 μM. The antagonism was probably not due to enhancement of endogenous cholinergic action, as it was not mimicked by acetylcholine, carbachol, or bethanechol; rather, it likely reflected a recently described interaction of THA with the phencyclidine receptor. Exploration of structural specificity revealed some partial neuron-protection with high concns. of other cholinesterase inhibitors (physostigmine, neostigmine, and edrophonium), but not the structurally related K channel blocker, 4-aminopyridine. Further examination of correlations between THA-like structure, and neuron-protective activity, may provide useful insights in the development of new antagonists of NMDA receptor-mediated neurotoxicity.
IT 321-64-2, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: BIOL (Biological study)
(methylaspartate receptor-mediated neurotoxicity inhibition by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



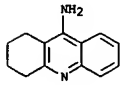
L11 ANSWER 215 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:542474 HCAPLUS
DOCUMENT NUMBER: 109:142474
TITLE: Interaction of 9-amino-1,2,3,4-tetrahydroaminoacridine (THA) with human cortical nicotinic and muscarinic receptor binding in vitro
AUTHOR(S): Perry, E. K.; Smith, C. J.; Court, J. A.; Bonham, J. R.; Rodway, M.; Atack, J. R.
CORPORATE SOURCE: Neuropathol., Newcastle Gen. Hosp., Newcastle upon Tyne, UK
SOURCE: Neuroscience Letters (1988), 91(2), 211-16
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB THA and physostigmine inhibited acetylcholinesterase with 50% inhibitory concentration (IC50) values of 7.9 + 10-7 and 4.5 + 0-8M, resp., in human cerebral cortex. In contrast, the IC50 values for [3H]nicotine displacement, a measure of nicotinic receptors, were 2 + 10-5 and 2 + 10-2M for THA and physostigmine, resp. The displacement of [3H]N-methylscopolamine from muscarinic receptors showed a similar 100-fold difference. Carbachol-stimulated myo-inositol hydrolysis, a measure of muscarinic receptor 2nd messenger activity, also was greater after THA. Thus, differences between these compds. may be related to receptor interactions and not enzyme inhibition.
IT 321-64-2
RL: BIOL (Biological study)
(acetylcholinesterase inhibition and cholinergic receptor binding by, in human cerebral cortex)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



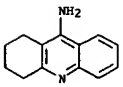
L11 ANSWER 216 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:506948 HCAPLUS
DOCUMENT NUMBER: 109:106948
TITLE: Estimation of cholinesterase activity (EC 3.1.1.7; 3.1.1.8) in undiluted plasma and erythrocytes as a tool for measuring in vivo effects of reversible inhibitors
AUTHOR(S): Thomsen, T.; Kewitz, H.; Pleul, O.
CORPORATE SOURCE: Inst. Klin. Pharmakol., Freie Univ. Berlin, Berlin, D-1000/45, Fed. Rep. Ger.
SOURCE: Journal of Clinical Chemistry and Clinical Biochemistry (1988), 26(7), 469-75
CODEN: JCCBDT; ISSN: 0340-076X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In vivo effects of reversible inhibitors of cholinesterase were determined radiometrically in undiluted samples of erythrocytes and plasma. [14C] acetylcholine at substrate saturation, 25°, and pH 7.4 permitted rapid and precise determination of butyrylcholinesterase (EC 3.1.1.8) and acetylcholinesterase (EC 3.1.1.7). Reference values for acetylcholinesterase and butyrylcholinesterase were estimated in the plasma and erythrocyte hemolyzate of healthy volunteers. The time course of in vitro inhibition was monitored, starting immediately after addition of 9-amino-1,2,3,4-tetrahydroacridine (tacrine), eserine, or pyridostigmine to undiluted human plasma. Maximal inhibition was in ≤60 min with tacrine and eserine, and in ≤180 min with pyridostigmine. The inhibition remained constant for >10 h except with eserine, from which enzyme activity showed an early recovery. Concentration response expts. were performed in undiluted human plasma and undiluted human erythrocyte hemolyzate. The Ki values of tacrine, eserine, and pyridostigmine were estimated In contrast to pyridostigmine and eserine, tacrine had higher affinity for butyrylcholinesterase than for acetylcholinesterase. Tacrine at 2.5 μM resulted in complete inhibition of butyrylcholinesterase and inhibition of acetylcholinesterase activity. Dilution of samples to ≤100-fold was accompanied by almost complete recovery of acetylcholinesterase and by 50% recovery of butyrylcholinesterase.
IT 321-64-2, Tacrine
RL: BIOL (Biological study)
(acetylcholinesterase and butyrylcholinesterase of human inhibition by, kinetics of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



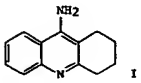
L11 ANSWER 217 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:448290 HCAPLUS
DOCUMENT NUMBER: 109:48290
TITLE: Characterization of the scopolamine stimulus in rats
AUTHOR(S): Jung, M.; Perio, A.; Worms, P.; Biziere, K.
CORPORATE SOURCE: Sanofi Rech., Montpellier, F-34082, Fr.
SOURCE: Psychopharmacology (Berlin, Germany) (1988), 95(2), 195-9
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The discriminative stimulus properties of scopolamine, a potent antagonist at muscarinic receptors, were used for testing the discriminative effects of drugs known to act on cholinergic transmission. Rats were trained in a standard 2-bar operant conditioning procedure with food as the reinforcer, according to a fixed ratio 10 schedule. The training dose of scopolamine was progressively reduced from 0.25 mg/kg, s.c. to the low dose of 0.062 mg/kg s.c. Scopolamine yielded an accurate discrimination in all the rats tested. The generalization gradient resulted in an ED50 of central origin, since it was not mimicked by scopolamine methylbromide. The scopolamine stimulus generalized to atropine and trihexyphenidyl (resp. ED50 values 2.20 and 0.21 mg/kg s.c.). Atropine depressed the rate of responding, while trihexyphenidyl did not. Antagonism both with direct agonists at the muscarinic receptor (arecoline and oxotremorine) and indirect agonists, i.e., inhibitors of the acetylcholine esterase (physostigmine and tetrahydroaminoacridine), led to inconsistent results. Increasing the doses of the agonists in order to block the scopolamine cue may be limited by their rate-suppressant effect on responding. Thus, the muscarinic agonist cue is more useful than the antagonist cue for investigating muscarinic transmission.
IT 321-64-2
RL: BIOL (Biological study)
(discriminative behavior from scopolamine response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 218 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:416984 HCAPLUS
DOCUMENT NUMBER: 109:16984
TITLE: Effects of tetrahydroaminoacridine on M1 and M2 muscarine receptors
AUTHOR(S): Pearce, Bradley D.; Potter, Lincoln T.
CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, 33133, USA
SOURCE: Neuroscience Letters (1988), 88(3), 281-5
CODEN: NELED5; ISSN: 0304-3940
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrahydroaminoacridine (THA) has been reported to improve the memory of persons with Alzheimer's disease, but its mechanism of action is uncertain. Clin. effective concns., 0.03-0.3 μM, readily inhibit acetylcholinesterase and butyrylcholinesterase from rabbit hippocampal tissue in artificial cerebrospinal fluid at 37° with physiol. levels of substrate. Above 1 μM, THA acts at primary and allosteric sites on M1 and M2 muscarine receptors as an antagonist. This is not clin. important, and low levels of THA do not improve the binding of the agonist, oxotremorine-M. Only 10-1000 μM THA has been shown to block K+ channels. Thus, THA probably acts as an esterase inhibitor.
IT 321-64-2, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: PRP (Properties)
(interaction of, with esterases and muscarinic receptors)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



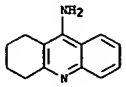
L11 ANSWER 219 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:124385 HCAPLUS
DOCUMENT NUMBER: 108:124385
TITLE: Further analysis of the neuropharmacological profile of 9-amino-1,2,3,4-tetrahydroacridine (THA), an alleged drug for the treatment of Alzheimer's disease
AUTHOR(S): Drukarch, B.; Leysen, J. E.; Stoof, J. C.
CORPORATE SOURCE: Med. Fac., Free Univ., Amsterdam, 1081 BT, Neth.
SOURCE: Life Sciences (1988), 42(9), 1011-17
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



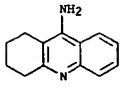
I

AB The effects of 9-amino-1,2,3,4-tetrahydroacridine (THA) (I) on the uptake and release of radiolabeled noradrenaline, dopamine, and serotonin by brain were studied. THA concentration-dependently inhibited the uptake of these monoamines with 50% inhibitory concentration values of approx. 1, 7 and 2 μM resp. Release studies of these radiolabeled monoamines from control and reserpine-pretreated tissue revealed that the THA-induced uptake inhibition does not occur at the level of the axonal membrane but at the level of the monoaminergic storage granules. In addition the affinity of THA for α-1, α-2 and β-adrenoceptors, for D-2 dopamine, S-1a and S-2 serotonin and for muscarinic receptors was investigated. It appeared that in concns. up to 1 μM, THA did not display any affinity towards these receptors. Apparently, the effects of THA on monoaminergic neurotransmission might contribute to the alleged therapeutic action of THA in Alzheimer's disease.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(monoaminergic neurotransmission in brain response to, Alzheimer's disease treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

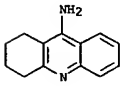
L11 ANSWER 219 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



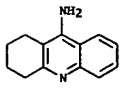
L11 ANSWER 220 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:31916 HCAPLUS
DOCUMENT NUMBER: 108:31916
TITLE: Do tetrahydroaminoacridine (THA) and physostigmine restore acetylcholine release in Alzheimer brains via nicotinic receptors?
AUTHOR(S): Nilsson, Lena; Adem, A.; Hardy, J.; Winblad, B.; Nordberg, A.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Uppsala, Uppsala, S-75124, Swed.
SOURCE: Journal of Neural Transmission (1972-1989) (1987), 70(3-4), 357-68
CODEN: JNTMAH; ISSN: 0300-9564
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the presence of 9-amino-1,2,3,4-tetrahydroacridine (THA) (10-4 M) or physostigmine (10-4 M), the in vitro [3H]acetylcholine ([3H]ACh) release from control human cortical slices was reduced. In contrast, THA and physostigmine increased the release of [3H]ACh in brain tissue from patients with Alzheimer's disease/senile dementia of Alzheimer's (AD/SDAT). This facilitating effect on [3H]-ACh release was partially blocked (50%) in the presence of the nicotinic antagonist d-tubocurarine (10-6 M), indicating a possible interaction via nicotinic receptors. The muscarinic antagonist atropine (10-5 M) increased the [3H]ACh release both in control and AD/SDAT brains, thus indicating preservation of muscarinic autoreceptors in the AD/SDAT cortical tissue. In receptor competition studies with [3H]nicotine, [3H]ACh and [3H]quinuclidinyl benzilate as receptor ligands, THA interfered with both nicotinic and muscarinic receptor ligand binding, whereas physostigmine had much less effect.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(acetylcholine release from brain cortex stimulation by, in Alzheimer's disease in human)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 221 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:31864 HCAPLUS
DOCUMENT NUMBER: 108:31864
TITLE: Tetrahydroaminoacridine blocks potassium channels and inhibits sodium inactivation in Myxicola
AUTHOR(S): Schauf, Charles L.; Sattin, Albert
CORPORATE SOURCE: Dep. Biol., Purdue Univ., Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1987), 243(2), 609-13
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In voltage-clamped Myxicola giant axons internally and externally applied tetrahydroaminoacridine (THA) blocked K+ channels with a dissociation constant of 100 μM and slowed their rate of activation. At a concentration of 10 μM, internal THA primarily slowed inactivation of conducting Na+ channels. At 100 μM the decline of the Na+ current during depolarizing pulses was biphasic, with an initial phase 2 to 3 times faster than in control axons. In the presence of THA there was a steady-state inward current accompanied by an increase in amplitude and time constant of Na+ tail currents, as if THA blocked Na+ channels by first entering them and then rendered THA-occluded channels resistant to fast inactivation. THA did not alter activation, prepulse-induced fast inactivation or slow inactivation. The effects of THA on voltage-dependent axonal ion channels might account for central nervous system hyperexcitability seen in some patients treated with THA. Because THA is a potent, centrally active anticholinesterase, even subtle ion channel-directed effects might contribute to its putative antidementia action in clin. states involving a central nervous system deficiency of acetylcholine by selective augmentation of acetylcholine release and/or negation of autoreceptor effects of endogenous acetylcholine.
IT 321-64-2, 1,2,3,4-Tetrahydro-9-aminoacridine
RL: BIOL (Biological study)
(potassium and sodium channels of nerve blockade by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

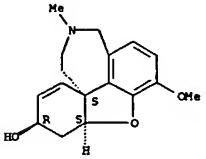


L11 ANSWER 222 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:590857 HCAPLUS
DOCUMENT NUMBER: 107:190857
TITLE: 9-Amino-1,2,3,4-tetrahydroacridine (THA), an alleged drug for the treatment of Alzheimer's disease, inhibits acetylcholinesterase activity and slow outward potassium current
AUTHOR(S): Drukarch, Benjamin; Kits, Karel S.; Van der Meer, Eric G.; Lodder, Johannes C.; Stoof, Johannes C.
CORPORATE SOURCE: Med. Fac., Free Univ., Amsterdam, 1081 BT, Neth.
SOURCE: European Journal of Pharmacology (1987), 141(1), 153-7
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vitro release of acetylcholine in rat brain tissue was inhibited by 9-amino-1,2,3,4-tetrahydroacridine (THA). Atropine antagonized this effect of THA. As THA does not display an affinity for muscarinic receptors, THA appears to inhibit acetylcholinesterase activity. In electrophysiol. studies with neurons of Lymnaea stagnalis, THA inhibited the slow outward K+ current and consequently increased the duration of the action potentials. Both effects of THA may possibly contribute to its reported effect in the treatment of patients with Alzheimer's disease.
IT 321-64-2, 9-Amino-1,2,3,4-tetrahydroacridine
RL: BIOL (Biological study)
(acetylcholinesterase of brain and neuron potassium current inhibition by, Alzheimer's disease treatment in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

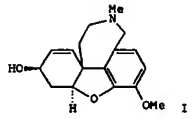


L11 ANSWER 223 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:451872 HCAPLUS
DOCUMENT NUMBER: 107:51872
TITLE: Study of the ability of reversible cholinesterase inhibitors to bring about dissociated learning in rats
AUTHOR(S): Azarashvili, A. A.; Arkhipov, V. I.; Budantsev, A. Yu.; Prozorovskii, V. B.
CORPORATE SOURCE: Inst. Biol. Fiz., Pushchino, USSR
SOURCE: Farmakologiya i Toksikologiya (Moscow) (1987), 50(3), 27-9
CODEN: FATOAO; ISSN: 0014-8318
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The reversible cholinesterase inhibitors galanthamine, eserine, and aminostigmine at 1/4-1/2 LD50 evoke a dissociated state in rats and bring about dissociated learning. The depression of simple, established alimentary
reflexes noted during administration of large doses of reversible inhibitors may be lifted by administration of a mixture of muscarinic and nicotinic cholinolytics. Ftoracizine, possessing 250-fold less affinity for muscarinic receptors of the bladder, is only slightly inferior to atropine in its ability to lift the dissociated state evoked by cholinesterase inhibitors.
IT 357-70-0, Galanthamine
RL: BIOL (Biological study)
(dissociated learning induced by, reversible inhibition of cholinesterase in relation to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 224 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:27326 HCAPLUS
DOCUMENT NUMBER: 106:27326
TITLE: Pharmacokinetics of galanthamine (a long-acting anticholinesterase drug) in anesthetized patients
AUTHOR(S): Westra, Pieter; Van Thiel, Martinus J. S.; Vermeer, Gustaff A.; Soeterbroek, Adrianus M.; Scaf, Arnoldus H. J.; Claessens, Henk A.
CORPORATE SOURCE: Inst. Anesthesiol., State Univ. Groningen, Groningen, Neth.
SOURCE: British Journal of Anaesthesia (1986), 58(11), 1303-7
CODEN: BJANAD; ISSN: 0007-0912
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

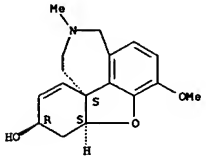


I

AB The pharmacokinetics of the long-acting anticholinesterase drug galanthamine (I) [357-70-0], (0.3 mg/kg, i.v.) were investigated in patients. After injection, a decrease in the serum concentration
of galanthamine followed a biexponential curve. The serum concentration decreased rapidly from 543 to 128 ng/mL between 2 and 30 min with an elimination half-life T1/2α of 6.42-2.15 min, and then declined more slowly with a T1/2β of 264 min. Total serum clearance of galanthamine was 5.37 mL/min/kg, and the renal clearance was 1.36 mL/min/kg. The cumulative urinary excretion of galanthamine between 0 and 48 h after injection was 28.0% of the administered dose. The biliary excretion of galanthamine during 24 h was 0.2% of the dose. There was no evidence of glucuronide or sulfate conjugation of galanthamine.
IT 357-70-0, Galanthamine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, in humans)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

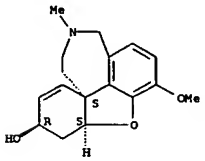
Absolute stereochemistry. Rotation (-).

L11 ANSWER 224 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



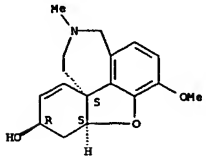
L11 ANSWER 225 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:418349 HCAPLUS
DOCUMENT NUMBER: 105:18349
TITLE: Effect of N- and M-cholinomimetics and cholinoblockers on epileptogenesis of the penicillin focus in dorsal hippocampus
AUTHOR(S): Losev, N. A.; Tkachenko, E. I.
CORPORATE SOURCE: Inst. Exp. Med., Leningrad, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1986), 101(4), 436-8
CODEN: BEBMAE; ISSN: 0365-9615
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB In rabbits with penicillin-induced epilepsy, i.v. injections of the acetylcholinesterase inhibitor galanthamine [357-70-0] (1 mg/kg) or the nicotinic (N)-cholinoblockers, gangleron [1510-29-8] (3 mg/kg) and Eterofen [13426-07-8] (8 mg/kg) decreased or completely suppressed epileptogenesis. Combination of galanthamine with either N-cholinoblocker markedly increased their anticonvulsive actions. On the contrary, combination of galanthamine with the muscarinic (M)-cholinoblocker metamisyl [10503-18-1] (0.5 mg/kg) enhanced epileptogenesis. Apparently, both M- and N-cholinergic mechanisms take part in the genesis of epilepsy. The use of N-cholinoblockers and their combinations with M-cholinomimetics as anticonvulsants is indicated.
IT 357-70-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticonvulsant activity of)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



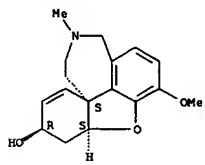
L11 ANSWER 226 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:200012 HCAPLUS
DOCUMENT NUMBER: 104:200012
TITLE: Neuropharmacological analysis of compensatory processes following lesions of the head of the caudate nucleus.
AUTHOR(S): Mukhin, E. I.
CORPORATE SOURCE: Brain Res. Inst. Natl. Sci. Cent. Psychic Health, Moscow, USSR
SOURCE: Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova (1986), 72(2), 152-7
CODEN: FZLZAM; ISSN: 0015-329X
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The ability of caudatectomized cats to recover lost ability to generalize and form elementary abstractions was studied with the aid of parenterally administered psychotropic agents. Studies of the effects of L-DOPA [59-92-7] (15 mg/kg), phenamine [60-13-9] (1 mg/kg), atropine [51-55-8] (0.3 mg/kg), galanthamine [357-70-0] (1 mg/kg), acetylcholine [51-84-3] plus proserine [51-60-5] (0.1 mg/kg), gammalon [56-12-2] (70 mg/kg), aminalon [56-12-2] (70 mg/kg), GABA [56-12-2] (70 mg/kg), and bicuculline [485-49-4] showed that lost abilities could be recovered with the aid of dopaminergic and, to a lesser extent, GABA-ergic agents.
IT 357-70-0
RL: BIOL (Biological study)
(mental function recovery response to, after lesion of head of caudate nucleus)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

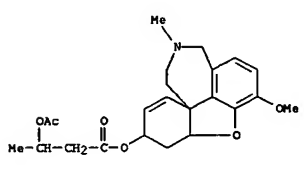


L11 ANSWER 227 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:552772 HCAPLUS
DOCUMENT NUMBER: 99:152772
TITLE: Presynaptic effects of armine and galanthamine on the mammalian neuromuscular junction
AUTHOR(S): Drabkina, T. M.; Kuleshov, V. I.; Matyushkin, D. P.; Sanotskii, V. I.; Sei, T. P.
CORPORATE SOURCE: State Univ., Leningrad, USSR
SOURCE: Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova (1983), 69(7), 906-12
CODEN: FZLZAM; ISSN: 0015-329X
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The effects of the phosphoorg. cholinesterase inhibitor armin [546-71-4] and the quaternary ammonium cholinesterase inhibitor galanthamine [357-70-0] on neuromuscular transmission and spontaneous and evoked acetylcholine [51-84-3] release in rat diaphragms were studied. High concns. of both inhibitors (≥10-6 g/mL) decreased the supply of accessible acetylcholine and consequently decreased the end-plate potential. During repetitive stimulation of the phrenic nerve (10-100 impulses/s) armin and galanthamine accelerated depression of the end-plate potential and slowed the rate of neurotransmitter mobilization. This inhibition of presynaptic function resulted in a rapid decrease in the quantum content and amplitude of end-plate potential. These presynaptic disturbances plus stationary postsynaptic depolarization may cause neuromuscular blockade.
IT 357-70-0
RL: BIOL (Biological study)
(acetylcholine release and neuromuscular transmission in diaphragm response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 228 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:506546 HCAPLUS
DOCUMENT NUMBER: 97:106546
TITLE: Identification and quantitative determination of m-hydroxyphenylglycol in mammalian urine
AUTHOR(S): Crowley, Jan R.; Couch, Margaret W.; Williams, Clyde M.; James, Michael I.; Ibrahim, Kamal E.; Midgley, John M.
CORPORATE SOURCE: Dep. Radiol., Univ. Florida Coll. Med., Gainesville, FL, 32610, USA
SOURCE: Biomedical Mass Spectrometry (1982), 9(4), 146-52
CODEN: BMSYAL; ISSN: 0306-042X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB m-Hydroxyphenylglycol was determined in mammalian urine by selected ion monitoring using a pentadeuterated internal standard The glycol was converted to its tris-pentafluoropropionyl derivative and identified by gas chromatog. retention times and the ions m/z 592, 428, and 415. The glycol was excreted as the sulfate conjugate (2-18 ng/mg creatinine in humans and 0.5-1.1 μg/day in rats). Urinary m-hydroxymandelic acid was also determined; the acid:glycol ratio was 1:1 in rat and 6:1 in human. Thus, the overall reductive path of m-octopamine and m-synephrine metabolism is more important in the rat than in the human.
IT 82660-84-2P
RL: PREP (Preparation)
(preparation of)
RN 82660-84-2 HCAPLUS
CN Butanoic acid, 3-(acetyloxy)-, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-yl ester, [4aS-[4aα,6β(R*),8aR*]]- (9CI) (CA INDEX NAME)

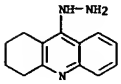


L11 ANSWER 229 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1980:440257 HCAPLUS
DOCUMENT NUMBER: 93:40257
TITLE: Kinetics of inhibition of acetylcholinesterase by 9-hydrazino-1,2,3,4-tetrahydroacridine and 9-amino-10-methyl-1,2,3,4-tetrahydroacridinium in vitro
AUTHOR(S): Patocka, Jiri; Bajgar, Jiri; Bielavsky, Jiri
CORPORATE SOURCE: Purkyne Med. Res. Inst., Hradec Kralove, 502 60, Czech.
SOURCE: Collection of Czechoslovak Chemical Communications (1980), 45(3), 966-76
CODEN: CCCCAK; ISSN: 0366-547X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The kinetics of inhibition of solubilized rat brain acetylcholinesterase (I) by 9-hydrazino-1,2,3,4-tetrahydroacridine (THH) and 9-amino-10-methyl-1,2,3,4-tetrahydroacridinium (QTHA) were determined; the inhibitory effect was compared with the effect of tacrine (9-amino-1,2,3,4-tetrahydroacridine, THA). THH is a reversible, noncompetitive inhibitor of rat brain I (Ki = 0.16 μM), and it binds, similarly to THA, to the hydrophobic domain of the active center of I, thus simultaneously inhibiting the formation of the inactive complex ES2 with acetylcholine as substrate. This eliminates the inhibition of I by excess substrate. QTHA is a mixed, competitive-noncompetitive inhibitor characterized by Ki (competitive) = 5.3 μM and Ki (noncompetitive) = 0.08 μM. QTHA binds to an entirely different site of the active surface of I than THA and THH. This binding site is most likely the so-called β-anionic or also peripheral anionic site to which, e.g., atropine is also bound. Both inhibitors studied form a reversible, enzymically inactive complex in which 1 inhibitor mol. is bound to each active center of I.

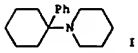
IT 74126-69-5
RL: BIOL (Biological study)
(acetylcholinesterase inhibition by, kinetics of)

RN 74126-69-5 HCAPLUS
CN Acridine, 9-hydrazino-1,2,3,4-tetrahydro-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

L11 ANSWER 230 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1980:361 HCAPLUS
DOCUMENT NUMBER: 92:361
TITLE: Some aspects of the pharmacology of phencyclidine
AUTHOR(S): Domino, Edward F.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Detroit, MI, 48207, USA
SOURCE: Psychopharmacol. Hallucinogens, [Workshop] (1978), Meeting Date 1976, 105-17. Editor(s): Stillman, Richard C.; Willette, Robert E. Pergamon: Elmsford, N. Y.
CODEN: 41KDAI
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



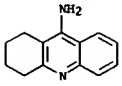
I

AB The effects of phencyclidine-HCl (I-HCl) [956-90-1] and 2 of its metabolites, 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (4-OH pip PCP) [60232-85-1] and 1-(1-phenyl-4-hydroxycyclohexyl)piperidine (4-OH cyclo PCP) [60756-83-4] were compared on rat locomotor activity and gross behavior in the dog. The 2 PCP metabolites produced some locomotor stimulation in the rat but were not as potent as I. The 4-OH pip PCP metabolite showed .apprx.1/10 the activity of I; 4-OH cyclo PCP was even less potent in increasing rat locomotor activity. In the dog 1.0 mg/kg i.v. I produced a biphasic response with an initial phase of anesthesia and a subsequent phase of severe emergence delirium; in larger doses anesthesia with convulsions was observed. Equimolar doses to 1.0 mg/kg I of 4-OH pip PCP caused only slight ataxia and disorientation, while 4-OH cyclo PCP showed no effect. However, in 10 times this dose 4OH cyclo PCP was a frank convulsant, while 4-OH pip PCP was a less intense convulsant and produced some disorientation like I. In the rat droperidol [548-73-2] (0.32 mg/kg i.p.) and 9-amino-1,2,3,4-tetrahydroacridine [321-64-2] (10 mg/kg i.p.) significantly reduced the locomotor stimulant effects of I. In the dog these agents in a dose of 1.0 mg/kg i.v. as pretreatment did not dramatically alter the I induced state. The plasma pharmacokinetics of I were determined in both the dog and monkey using gas chromatog.-mass fragmentog. in the electron impact mode (GC-MF-EI). In both species I (1 and 1.1 mg/kg i.v.) produced a complex exponential decline in the plasma levels with up to 2-3 phases. Compared to the monkey, the dog exhibited a pronounced emergence delirium during which time significant I plasma levels were detected. Very preliminary observations suggest that acidification of the urine in some human subjects may enhance urinary excretion of I.

IT 321-64-2
RL: BIOL (Biological study)
(behavioral effects of phencyclidine in response to)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 230 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



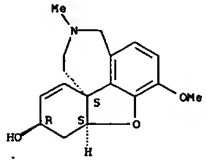
L11 ANSWER 231 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1978:502635 HCAPLUS
DOCUMENT NUMBER: 89:102635
TITLE: Properties of human erythrocyte acetylcholinesterase modified by N,N-dimethyl-2-phenylaziridinium ions
AUTHOR(S): Volkova, R. I.; Kochetova, L. M.
CORPORATE SOURCE: I. M. Sechenov Inst. Evol. Physiol. Biochem., Leningrad, USSR
SOURCE: Bioorganicheskaya Khimiya (1978), 4(5), 699-706
CODEN: BIKHD7; ISSN: 0132-3423
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB Acetylcholinesterase (I) was incubated 4 h with N,N-dimethyl-2-phenylaziridinium (1 + 10-3M), which alkylates the anionic sites, and the resulting modified enzyme was studied in respect to its thermostability and catalytic properties. Modified I fails to hydrolyze acetylcholine, but cleaves the noncharged substrate, indophenylacetate, at a higher rate than does native I. Monoquaternary and some polymethylenebisquaternary inhibitors exert no effect on modified I, which is also insensitive to the nature of cationic group in the leaving portion of the organophosphorus inhibitors. Cationic compds. having bulky aromatic groups (galanthamine, pancuronium, etc.) are much less effective inhibitors of the modified than native forms of I. When studying inhibitory activity of enantiomeric organophosphorus compds., CH3(C2H5O)P(O)SR, a considerable loss in stereospecificity of the esterase site was revealed in modified I. The stereospecificity of the latter is of the same order as that of butyrylcholinesterase. It is hypothetically suggested that modified I might represent a conformationally restricted form corresponding to the initial stage of ionic binding of cationic substrates or inhibitors.

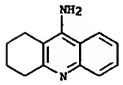
IT 357-70-0
RL: BIOL (Biological study)
(acetylcholinesterase inhibition by, chemical modification effect on)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



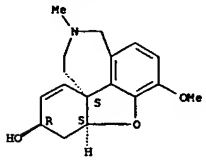
L11 ANSWER 232 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1978:182724 HCAPLUS
DOCUMENT NUMBER: 88:182724
TITLE: On the interaction of drugs with the cholinergic nervous system. V. Characterization of some effects induced by physostigmine in mice: in vivo and in vitro studies
AUTHOR(S): Maayani, Saul; Egozi, Yaakov; Pinchasi, Irit; Sokolovsky, Mordechai
CORPORATE SOURCE: Dep. Biochem., Tel Aviv Univ., Tel Aviv, Israel
SOURCE: Biochemical Pharmacology (1978), 27(2), 203-11
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dose-response curves obtained from simultaneous measurements of the salivation, tremor, hypothermia, and rotarod-effects induced by s.c. injection of physostigmine salicylate (I) (0.12-1.45 μmol/kg) and neostigmine bromide (II) (0.02-0.6 μmol/kg) showed a good relation to the dose-response curve for brain acetylcholinesterase (III) inhibition by I and II. The relative potencies of I and II and their affinity for III were also related. (-)-Scopolamine-HBr antagonized the salivation and hypothermia induced by I and II completely, and the rotarod effects by 80%, but scopolamine methiodide only antagonized the salivation. The tremor induced by I, II, and tacrine-HCl was not blocked by scopolamine-HBr or its analog, whereas that induced by acetylcholine-like muscarinic tertiary drugs was completely blocked. I-induced hypothermia was probably a central-muscarinic response, whereas the tremor was probably a nonmuscarinic peripheral effect. The rotarod effects were muscarinic and mixed central-peripheral for I, and nonmuscarinic for II. I-induced salivation was a peripheral-muscarinic effect. The lethality caused by I may be centrally mediated whereas that of II was peripheral.
IT 1684-40-8
RL: BIOL (Biological study)
(tremor from, scopolamine effect on)
RN 1684-40-8 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L11 ANSWER 233 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1978:83654 HCAPLUS
DOCUMENT NUMBER: 88:83654
TITLE: Neuromuscular effects of galanthamine versus neostigmine and hexafluorenium
AUTHOR(S): Baraka, Anis
CORPORATE SOURCE: Dep. Anesthesiol., American Univ. Beirut, Beirut, Lebanon
SOURCE: International Congress Series (1975), Volume Date 1974, 347(Recent Prog. Anaesthesiol. Resusc., Proc. Eur. Congr. Anaesthesiol., 4th), 255-60
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The anticholinesterases neostigmine [59-99-4] (1-2mg) and galanthamine [357-70-0] (20-40 mg) did not depress neuromuscular transmission in human subjects, whereas hexafluorenium [317-52-2] produced a significant neuromuscular block. In contrast with hexafluorenium, the 2 other anticholinesterases reversed a blocking dose of tubocurarine [57-94-3]. Neostigmine and galanthamine exaggerated the muscarinic side effects of suxamethonium [306-40-1], whereas hexafluorenium prolonged its action and modified its blocking activity.
IT 357-70-0
RL: BIOL (Biological study)
(nerve-muscle transmission response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



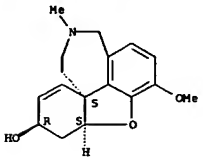
L11 ANSWER 234 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1977:593791 HCAPLUS
DOCUMENT NUMBER: 87:193791
TITLE: Antagonism by cholinergic drugs of behavioral effects in cats of an anticholinergic psychotomimetic drug and enhancement by nicotine
AUTHOR(S): Lowy, K.; Abood, M. E.; Drexler, M.; Abood, L. G.
CORPORATE SOURCE: Med. Cent., Univ. Rochester, Rochester, NY, USA
SOURCE: Neuropharmacology (1977), 16(6), 399-403
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-methyl-4-piperidylisopentynylphenyl glycollate (I) [16862-13-8] (10-25 μg/kg, s.c.) modified the number of responses and the lateral preference for the use of left or right levers of cats trained to press a lever for a food reward in response to an auditory stimulus. Administration of physostigmine-HCl [6091-12-9] (50 μg/kg, s.c.) or 1,2,3,4-tetrahydroaminoacridine-HCl [1684-40-8] (100 μg/kg, s.c.) with I caused both parameters to return to normal. Arecoline-HCl [61-94-9] (100 μg/kg, s.c.) had a slight antagonistic effect, while nicotine-HCl [2820-51-1] (100 μg/kg, s.c.) enhanced the effect of I. The behavioral effects of I must involve muscarinic neurons.
IT 1684-40-8
RL: BIOL (Biological study)
(glycolate ester-induced behavior inhibition by)
RN 1684-40-8 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)

● HCl

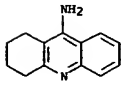
L11 ANSWER 235 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1976:539101 HCAPLUS
DOCUMENT NUMBER: 85:139101
TITLE: Interaction of reversible inhibitors with catalytic centers and allosteric sites of cholinesterases
AUTHOR(S): Tonkopii, V. D.; Prozorovskii, V. B.; Suslova, I. M.
CORPORATE SOURCE: S. M. Kirov Mil. Med. Acad., Leningrad, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1976), 82(8), 947-50
CODEN: BEBMAE; ISSN: 0365-9615
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The kinetics of inhibition of human erythrocyte acetylcholinesterase with galanthamine, tacrine, and oxazyl and the effects of these reversible inhibitors on chick, mouse, cat, and rat blood plasma enzyme were studied. Galanthamine caused an increase in the Km for acetylcholine and was a competitive inhibitor. It apparently binds in the enzyme active site. Tacrine decreased the Vmax, had no effect on Km, and was a noncompetitive inhibitor. It binds at a noncatalytic site on the enzyme, possibly in a hydrophobic region. Oxazyl changed the shape of the activity-substrate concentration curve from hyperbolic to sigmoidal and thus binds at the allosteric anionic site of the enzyme.
IT 321-64-2
RL: BIOL (Biological study)
(acetylcholinesterase inhibition by)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

L11 ANSWER 236 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1976:504081 HCAPLUS
DOCUMENT NUMBER: 85:104081
TITLE: Study of the reaction of galanthamine with the acetylcholinesterase of the mouse brain in vivo
AUTHOR(S): Tonkopii, V. D.; Prozorovskii, V. B.
CORPORATE SOURCE: S. M. Kirov Mil. Med. Acad., Leningrad, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1976), 82(7), 823-5
CODEN: BEBMAE; ISSN: 0365-9615
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The inhibitory effect of galanthamine [357-70-0] (10-6M in vitro; 4 mg/kg, i.p. in vivo) on mouse brain acetylcholinesterase [9000-81-1] was decreased by armin (3 + 10-6M and 0.33 mg/kg, s.c.). The in vivo effect was associated with an accumulation of acetylcholine which displaced galanthamine from the active center of the enzyme, suggesting competitive interaction between the enzyme and its inhibitor.
IT 357-70-0
RL: BIOL (Biological study)
(acetylcholinesterase interaction with)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

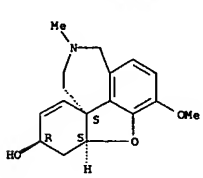


L11 ANSWER 237 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1975:80374 HCAPLUS
DOCUMENT NUMBER: 82:80374
TITLE: Pharmacology of 1,2,3,4-tetrahydro-9-aminoacridine
AUTHOR(S): Pusek, J.; Patocka, J.; Bajgar, J.; Bielavsky, J.; Herink, J.; Hrdina, V.
CORPORATE SOURCE: Purkyne Med. Res. Inst., Hradec Kralove, Czech.
SOURCE: Activitas Nervosa Superior (1974), 16(3), 226
CODEN: ACNSAX; ISSN: 0001-7604
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB 1,2,3,4-Tetrahydro-9-aminoacridine (I) [321-64-2] (1 + 10-6M) increased the contraction of the elec. stimulated rat diaphragm, having an effect similar to that of physostigmine [57-47-6]. I antagonized the effect of 3-quinuclidyl benzilate in the isolated rat jejunum. I had neg. inotropic and pos. chronotropic effects on the rat heart atria. The inhibition of acetylcholinesterase (EC 3.1.1.7) [9000-81-1] and cholinesterase (EC 3.1.1.8) [9001-08-5] by I was irreversible and noncompetitive. Thus, the antidotal effect of I in psychotomimetic poisoning may result from a direct effect of I on cholinergic receptors or from inhibition of acetylcholinesterase resulting in acetylcholine accumulation at cholinergic receptors.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 238 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1973:461560 HCAPLUS
DOCUMENT NUMBER: 79:61560
TITLE: Cholinergic mechanisms of memory. Analysis of the amnesic effect of anticholinergic drugs
AUTHOR(S): Il'yuchenok, R. Yu.; Eliseeva, A. G.
CORPORATE SOURCE: Inst. Physiol., Novosibirsk, USSR
SOURCE: International Journal of Psychobiology (1972), 2(3), 177-92
CODEN: IJPBBS; ISSN: 0020-7586
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Scopolamine (I) [51-34-3] (1-3 mg/kg) and benzacine [71-79-4] (10 mg/kg) administered i.v. 5 min before the experiment impaired the conditioning of the passive avoidance response in a 1-trial procedure in rats. The amnesic effect was much weaker when the compds. were injected immediately after training. As a result, consolidation is possible when the animals are trained under the influence of anticholinergic drugs. In this case, to attain an amnesic effect, high drug doses were required to ensure a more complete blockade of cholinoreceptors. When the conditioned emotional response of fear was elaborated in a ten-trial procedure, trace formation was possible against the background of the effect of 1-20 mg benzacine/kg. The possibility of abolishing traces of short-term and long-term memory under different degrees of blockade of cholinergic brain structures was studied in dogs. Benactyzine-HCl [57-37-4], 0.5 mg/kg, given 1-5 days after training, abolished the conditioned emotional fear response. To inhibit the response 3 weeks after its acquisition, massive prolonged blockade of the cholinoreactive structures was required (10 mg/kg twice a day for 3 days). The amnesic effect of the anticholinergics apparently was not due to their influence on registration stage. The degree of blockade of the cholinergic structures at the moment of trace formation may be the determining factor in the mechanism of the effect of anticholinergics on recent memory. When the stimulus strength or when the number of training sessions is increased, the blockade of the receptors may prove to be ineffective in consequence of their deblockade by high concentration of endogenous acetylcholine released.
IT 357-70-0
RL: BIOL (Biological study)
(memory response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



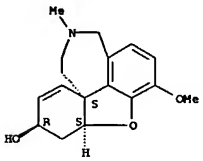
L11 ANSWER 238 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 239 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1972:54273 HCAPLUS
DOCUMENT NUMBER: 76:54273
TITLE: Chemical specificity of synapses in the frog midbrain tectum
AUTHOR(S): Vinogradova, V. M.; Smirnov, G. D.
CORPORATE SOURCE: A. N. Severtsov Inst. Evol. Morphol. Ecol. Anim., Moscow, USSR
SOURCE: Neirofiziologiya (1971), 3(4), 386-93
CODEN: NEFZBZ; ISSN: 0028-2561
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB Perfusion of isolated frog (Rana temporaria) heads with low concns. of the anticholinesterase agents, galanthamine [357-70-0] and eserine [57-47-6], increased the 1st and 2nd postsynaptic components of potentials of the midbrain tectum evoked by stimulation of the optic tract commissural fibers which occur as a result of activation of both myelinated and unmyelinated fibers. Higher concns. of these drugs at first increased these components then reversibly inhibited them. The anticholinergic agent, amizil [57-37-4], partly or completely, but reversibly, blocked both components. Gangleron [1510-29-8] did not affect evoked potentials. The anticholinesterase agents antagonized the effect of amizil. When both optic nerves were simultaneously subjected to tetanic stimulation, a substance similar to acetylcholine [51-84-3] was found in the perfusate. Apparently, optic terminals in the midbrain tectum form cholinergic synapses and the corresponding postsynaptic structures have muscarinic-type cholinoreceptors. Some variations in the dynamic changes in the 1st and 2nd postsynaptic components observed under the effect of both galanthamine and eserine as well as amizil indicated a higher sensitivity of synaptic systems composed of unmyelinated optic fibers. In contrast to optic terminals, transcommissural connections form no cholinergic synapses, and anticholinesterase and anticholinergic agents produced no effect on transcommissural potentials.

IT 357-70-0
RL: BIOL (Biological study)
(midbrain tectum synapses in response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

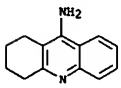


L11 ANSWER 239 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L11 ANSWER 240 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1972:54201 HCAPLUS
DOCUMENT NUMBER: 76:54201
TITLE: Metabolism of morphine N-oxide
AUTHOR(S): Heimans, R. L. H.; Fennessy, M. R.; Gaff, G. A.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Melbourne, Parkville, Australia
SOURCE: Journal of Pharmacy and Pharmacology (1971), 23(11), 831-6
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The opiates found in the urine of rats given morphine N-oxide (I) [639-46-3] (50 mg/rat, i.p.) were morphine [57-27-2] (61%) and I (39%). After morphine (20 mg/rat, i.p.) treatment, the urinary opiates were morphine (80%) and normorphine [466-97-7] (20%). After simultaneous administration of tacrine [321-64-2] and morphine, the urinary opiates were morphine (53%), normorphine (1%) and I (46%). Both tacrine and amiphenazole [490-55-1] decreased demethylation of morphine and codeine [76-57-3] by a rat liver microsomal plus soluble fraction. I and codeine N-oxide [3688-65-1] were not demethylated by the rat liver homogenate. I may be an intermediate metabolite of morphine whose excretion is increased by tacrine or amiphenazole because of inhibition of further metabolism.

IT 321-64-2
RL: BIOL (Biological study)
(morphine metabolism in response to, morphine oxide formation in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

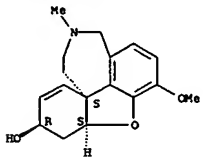


L11 ANSWER 241 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1972:54172 HCAPLUS
DOCUMENT NUMBER: 76:54172
TITLE: Response augmentation and blockade in cholinergic neuromuscular tissues
AUTHOR(S): Friess, S. L.
CORPORATE SOURCE: Nav. Med. Res. Inst., Bethesda, MD, USA
SOURCE: Neurosciences Research (New York) (1969), 2, 203-28
CODEN: NSREAS; ISSN: 0077-7846
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A discussion and review of interactions between cholinergic neuromuscular chemoreceptor loci and chems. which trigger overt responses, such as curare [7168-64-1], tropine [120-29-6], galanthamine [357-70-0], and muscarine [300-54-9]. 30 Refs.

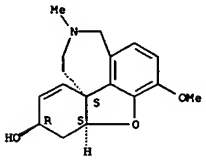
L11 ANSWER 242 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1971:539261 HCAPLUS
DOCUMENT NUMBER: 75:139261
TITLE: Effect of phenelzine on the toxicity of cholinergic drugs modified by reserpine
AUTHOR(S): Liebmann, H.; Matthies, H.; Kunbier, E.
CORPORATE SOURCE: Inst. Pharmakol. Toxikol., Med. Akad. Magdeburg, Magdeburg, Fed. Rep. Ger.
SOURCE: Acta Biologica et Medica Germanica (1971), 26(3), 551-8
CODEN: ABMGAJ; ISSN: 0001-5318
DOCUMENT TYPE: Journal
LANGUAGE: German
GI For diagram(s), see printed CA Issue.
AB In rats, the increase in the toxicity of cholinerigc drugs, such as acetylcholine, carbachol, physostigmine, diisopropyl fluorophosphate, and prostigmine caused by 5 mg reserpine/kg i.p. could be reduced or abolished by pretreatment with 20 mg of the reserpine inhibitor phenelzine (I)/kg, i.p. Reserpine slightly increased the toxicity of the cholinesterase inhibitor galanthamine, but did not affect that of paraoxon, and I pretreatment had no significant effect on these results. The role of the adrenergic nervous system in cholinergic mechanisms was discussed.
IT 357-70-0
RL: PRP (Properties)
(toxicity of, phenelzine effect on reserpine-induced)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

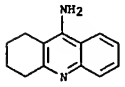


L11 ANSWER 243 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1971:417993 HCAPLUS
DOCUMENT NUMBER: 75:17993
TITLE: Action of anticholinesterase substances on cholinoreception in the superior cervical sympathetic ganglion of the cat
AUTHOR(S): Savateev, N. V.; Sofronov, G. A.
CORPORATE SOURCE: Voenno-Med. Akad. im. Kirova, Leningrad, USSR
SOURCE: Farmakologiya i Toksikologiya (Moscow) (1971), 34(2), 140-4
CODEN: FATOAO; ISSN: 0014-8318
DOCUMENT TYPE: Journal
LANGUAGE: Russian
GI For diagram(s), see printed CA Issue.
AB Armin (I) and O-pinacolyl-S-(β-ethylthioethyl)methylthiolophosphonate (II) increased the sensitivity of cat superior cervical sympathetic ganglion to acetylcholine and methylfurmethide 20-100-fold and to nicotine only 2-fold. The initial activity of nicotine during complete inhibition of ganglion cholinesterase was completely restored 2.5 hr after I and II administration. Galanthamine (III) reversibly increased the ganglion sensitivity to acetylcholine. Pralidoxime iodide (IV) reactivated I-inhibited cholinesterase in the ganglion and restored normal sensitivity to cholinomimetics. In the absence of cholinesterase reactivation in ganglia treated with II, IV did not increase sensitivity of the ganglia to acetylcholine and methylfurmethide but did accelerate restoration of normal sensitivity to nicotine.
IT 357-70-0
RL: BIOL (Biological study)
(nerve sensitivity to acetylcholine after armin administration reversal by)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

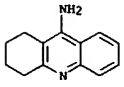
Absolute stereochemistry. Rotation (-).



L11 ANSWER 244 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1971:40971 HCAPLUS
DOCUMENT NUMBER: 74:40971
TITLE: Diuretic activity of tetrahydroaminacrin in rats
AUTHOR(S): Howland, John C.; Carter, M. Kathleen
CORPORATE SOURCE: Dep. of Pharmacol., Tulane Univ., New Orleans, LA, USA
SOURCE: Proceedings of the Society for Experimental Biology and Medicine (1970), 134(2), 513-16
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English
AB THA (tetrahydroaminacrine) administered s.c. caused a dose-related diuresis in rats. This diuretic response was probably not due to a muscarinic action of THA, as the diuresis was not blocked by atropine. Preliminary expts. in the dog and the chicken indicate that in these species there was little if any direct renal effect. The diuretic response to THA in rats does not appear to involve release of a pituitary hormone since hypophysectomy did not abolish the diuretic effect of THA.
IT 321-64-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diuretic activity of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



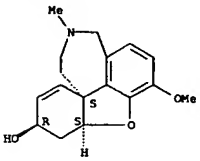
L11 ANSWER 245 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1970:507885 HCAPLUS
DOCUMENT NUMBER: 73:107885
TITLE: Facilitatory drug action on the isolated phrenic nerve-diaphragm preparation of the rat
AUTHOR(S): Freeman, Shirley E.; Turner, Raymond Jeffry
CORPORATE SOURCE: Def. Std. Lab., Aust. Def. Sci. Serv., Maribyrnong, Australia
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1970), 174(3), 550-9
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The action of facilitatory drugs was studied in the phrenic nerve-diaphragm preparation and the chronically denervated diaphragm of the rat. The latter was used as a model of the postsynaptic receptor. The drugs were tetrahydro-4-aminoacridine and a series of hydroxyanilinium compds. which included edrophonium. The drugs caused twitch potentiation and spontaneous activity in the intact preparation; these effects were depressed by temperature reduction, low Ca2+ solns. or high Mg2+ solns. The acetylcholine contraction of the denervated diaphragm was potentiated by all drugs except 3-hydroxyphenyltriethylammonium. The acetylcholine depolarization was similarly affected. This potentiation was suppressed by increased levels of Ca2+ or Mg2+. Succinylcholine abolished twitch potentiation of the intact preparation at low concns.; only 3-hydroxyphenyldiethylmethylammonium proved to be an effective antagonist of succinylcholine blockade. Facilitation in the intact junction appears to be largely a presynaptic effect.
IT 1684-40-8
RL: BIOL (Biological study)
(muscle-nerve junction in response to)
RN 1684-40-8 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

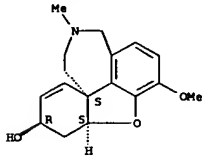
L11 ANSWER 246 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1970:454512 HCAPLUS
DOCUMENT NUMBER: 73:54512
TITLE: M-Cholinoreactive structures of the brain and conditioned activity
AUTHOR(S): Krylov, S. S.; Vinogradov, V. V.; Kal'ning, S. A.; Snegirev, E. A.
CORPORATE SOURCE: Inst. Toxicol., Leningrad, USSR
SOURCE: Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova (1970), 20(3), 541-6
CODEN: ZVNDAM; ISSN: 0044-4677
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Amizil in single administrations of 10 and 40 mg/kg prevented arecoline tremor in rats, arecoline and galanthamine electroencephalogram (EEG) desynchronization in cats, and evoked unmotivated motor excitation, caused complete disappearance of conditioned reflexes, and decreased noradrenaline content in rat brain. With repeated daily injections of 1 of the cholinolytics, the motor excitation, disturbances in conditioned reflexes, and decreased cerebral noradrenaline level gradually weakened and were not observed at all on the 9th-10th day, even though each successive amizil injection exerted the usual action on cat EEG and completely prevented desynchronization reaction in cats and tremor in rats. At the same time new conditioned reflexes did not form in the brain during complete block of the M-cholinoreceptors. The acetylcholine transmitter system in brain units seems to be significantly important in memory formation but is not necessary for the performance of preformed conditioned reactions.
IT 357-70-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brain response to, amizil effect on)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 247 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1970:443354 HCAPLUS
DOCUMENT NUMBER: 73:43354
TITLE: Distribution of galanthamine and securinine in the organs of poisoned animals
AUTHOR(S): Mikhno, V. V.; Kramarenko, V. F.
CORPORATE SOURCE: Lvov Med. Inst., Lvov, USSR
SOURCE: Farmatsevtichnii Zhurnal (Kiev) (1970), 25(1), 68-71
CODEN: FRZKAP; ISSN: 0367-3057
DOCUMENT TYPE: Journal
LANGUAGE: Ukrainian
AB Two groups of 4 dogs each were poisoned with 100 mg/kg body weight of galanthamine (I)-HBr and securinine (II) nitrate. Dogs died 1.5-2 hr after administration of the alkaloids. The distribution of I and II was then examined in the internal organs, blood, excrements, and vomited mass. The alkaloids were extracted with a H2SO4 solution of pH 2.5 and determined by known procedures. The highest level of both alkaloids was detected in vomited mass and urine. Smaller amts. occurred in stomach, intestine, liver, kidneys, brain, heart, and lungs. Unlike II, I was also detected in blood. It is concluded that for toxicol. examination the most suitable objects are vomited mass, stomach with its contents, liver, kidneys, and urinary bladder with urea.
IT 1953-04-4
RL: BIOL (Biological study)
(of tissues in poisoning)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

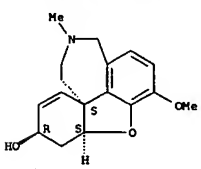
Absolute stereochemistry. Rotation (-).



● HBr

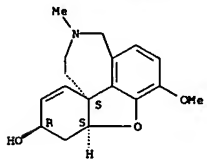
L11 ANSWER 248 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1970:118872 HCAPLUS
DOCUMENT NUMBER: 72:118872
TITLE: Effect of pharmacological agents on the growth of neuroblasts in culture
AUTHOR(S): Olenev, S. N.
CORPORATE SOURCE: Leningrad. Pediat. Med. Inst., Leningrad, USSR
SOURCE: Arkhiv Anatomii, Gistologii i Embriologii (1969), 57(9), 19-29
CODEN: AAGEAA; ISSN: 0004-1947
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB The effect of pharmacol. agents and prepns. on the morphol. of cultured neuroblasts and on the acetylcholin esterase level was studied. The tissues of the forebrain and the midbrain of a 10 day old chick embryo were cultured on a collagen medium for 3-10 days. The min. dose totally inhibiting the culture growth, as well as a maximum dose promoting the growth of the neuroblasts were determined by diluting the pharmacol. preparation in the nutrient medium. Acetylcholine, carbocholine, and cytisine significantly increased the acetylcholinesterase activity; proserine, galantamine, and armin inhibited the activity. Serotonin and substances with serotonin-like activity, as well as aminazin produced a rounding of the cells and inhibition of growth of some types of neuroblasts. However, aminazin did not lower the acetylcholinesterase activity, while serotonin caused a decrease. Long-term culturing with serotonin showed defects in nucleoli of the glial cells and changes in the bordering membrane structures. Strychnine depressed considerably the development of individual growth processes of the neuroblasts; picrotoxin revealed rare neuroblasts tolerant to large doses; histamine and piperoxal caused some swelling on the neuroblast bodies. Expts. with perfusion chambers revealed different reactions of the growing neuroblasts with atropine, aminazin, and serotonin.
IT 357-70-0
RL: BIOL (Biological study)
(nerves of chick embryos in response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 249 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1969:522066 HCAPLUS
DOCUMENT NUMBER: 71:122066
TITLE: Dependence of the action of neostigmine, nivaline, and paraoxon upon the frequency of stimulation
AUTHOR(S): Walther, Heinz
CORPORATE SOURCE: Med. Akad. "Carl Gustav Carus", Dresden, Fed. Rep. Ger.
SOURCE: Acta Biologica et Medica Germanica (1969), 22(5-6), 767-78
CODEN: ABMGAJ; ISSN: 0001-5318
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The anticholinesterase activities of neostigmine, nivaline, and paraoxon, at the neuromuscular junction of a rat diaphragm-phrenic nerve preparation were more dependent on the frequency of elec. stimulation (0.3-5 cycles/sec.) of the preparation than on the concentration (3 + 10-8 to 3 + 10-4M) of the cholinesterase inhibitor. By reducing the interval of stimulation to 150 msec., it was possible to completely abolish the contraction amplitude-increasing effect of the cholinesterase inhibitors. The anticholinesterase agents apparently caused an improved time-dependent mobilization of acetylcholine in the terminal region of the motor nerve fiber.
IT 1953-04-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neuromuscular junction response to, frequency of stimulation in relation to)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

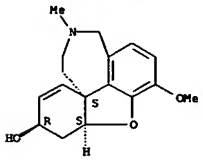
Absolute stereochemistry. Rotation (-).



● HBr

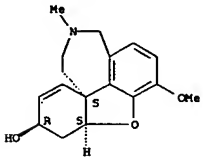
L11 ANSWER 250 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1969:500248 HCAPLUS
DOCUMENT NUMBER: 71:100248
TITLE: Effect of acetylcholine, anticholinesterases and cholinolytic agents on the vessels of an isolated rabbit heart
AUTHOR(S): Nikitin, A. I.
CORPORATE SOURCE: USSR
SOURCE: Probl. Klin. Eksp. Med. (1967), 354-5. Editor(s): Neimark, I. I. Altai. Knizhnoe Izd.: Barnaul, USSR. CODEN: 21FSAG
DOCUMENT TYPE: Conference
LANGUAGE: Russian
AB The modification of the coronary constriction effect of acetylcholine (I) by various compds. (concns. in mg./l. given in parentheses) were studied in the isolated perfused rabbit heart. I at concns. 20, 50, 200, and 1000 mg./l. caused 19.3, 49.4, 50.3, and 54.6% decreases in blood flow. The vasoconstricting effects of proserine (40-200), Galantamin (50-100), Phosphacol (10), and Armin (10) were less pronounced, and were synergistic to those of I (20). Atropine (20) did not prevent the effect of I, contrary to platyphylline (10-20), and Gastripon (10-20)
IT 357-70-0
RL: BIOL (Biological study)
(heart circulation response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



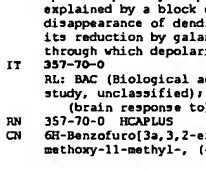
L11 ANSWER 251 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1969:437337 HCAPLUS
DOCUMENT NUMBER: 71:37337
TITLE: Sensitization of striated muscle choline receptors to acetylcholine
AUTHOR(S): Prozorovskii, V. B.
CORPORATE SOURCE: Leningrad Pediat. Med. Inst., Leningrad, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1969), 67(4), 56-9
CODEN: BEBMAE; ISSN: 0365-9615
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Sensitivity of the abdominal muscle of Rana temporaria to acetylcholine was increased by nibufin, physostigmine, phosphacol, galantamine, prostigmine, armin, and oxazyl. The increase was caused by decrease of cholinesterase activity and by increased sensitivity of choline receptors of the muscle.
IT 357-70-0
RL: BIOL (Biological study)
(muscle contraction by acetylcholine and)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



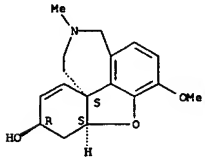
L11 ANSWER 252 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1969:85947 HCAPLUS
DOCUMENT NUMBER: 70:85947
TITLE: Comparison of the effects produced by anticholinergics and anticholinesterases on induced potentials of the cerebral cortex
AUTHOR(S): Il'yuchenok, R. Yu.; Zinevich, V. S.; Loskutova, L. V.
CORPORATE SOURCE: Ist. Fiziol., Novosibirsk, USSR
SOURCE: Farmakologiya i Toksikologiya (Moscow) (1969), 32(1), 3-7
CODEN: FATOAO; ISSN: 0014-8318
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Application of muscarinic anticholinergic substances to the cerebral cortex of cats inhibited the dendrite potential and the neg. variation in the reticulocortical response, while the amplitude of the specific primary response increased. Benactyzine or atropine administered i.v. inhibited the reticulocortical responses and significantly depressed the dendrite potentials, while the amplitude of the primary response somewhat increased. Galanthamine antagonized the changes in reticulocortical and dendrite responses induced by the muscarinic anticholinergic substances. There was no similar antagonism on the specific primary response. If the changes in neg. primary response can be explained by a block of the inhibited synapses, then the complete disappearance of dendrite potential during application of benactyzine and its reduction by galanthamine may be due to a block of axo-dendrite synapses through which depolarization of the surface layer dendrite occurs.
IT 357-70-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brain response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 253 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1969:36296 HCAPLUS
DOCUMENT NUMBER: 70:36296
TITLE: Effect of cholinergic substances on the bioelectric activity of the limbic system
AUTHOR(S): Il'yuchenok, R. Yu.; Bannikov, G. N.
CORPORATE SOURCE: Inst. Physiol., Novosibirsk, USSR
SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1968), 66(12), 55-60
CODEN: BEBMAE; ISSN: 0365-9615
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Eserine (0.3 mg./kg.), galanthamine (3 mg./kg.), arecoline (0.3 mg./kg.), nicotine (0.3 mg./kg.), or oxotremorine (0.5 mg./kg.) administered i.v. to rabbits caused the appearance of θ-rhythm on the electro-encephalogram (EEG) of the hippocampus, septum, medial and posterior limbic gyrus, cortical optic lobe, and pontomesencephalic reticular formation. A rapid low-amplitude rhythm was recorded on the EEG of the cortical sensomotor region, of the medial part of the limbic gyrus, and amygdala complex. The EEG-activation reactions were blocked by amizyl (0.6-1 mg./kg. i.v.) or benzacine (1-3 mg./kg. i.v.). The premesencephalic region did not eliminate the θ-rhythm induced by the anticholinesterase and cholinomimetic substances in the limbic system structures and in a cut off reticular formation, while slow high-amplitude waves remained in the neocortex. Disruption of the posterior hypothalamus to the premesencephalic regions prevented the development of the θ-rhythm in the limbic system. The limbic system apparently has the characteristic muscarinic (M-cholinergic) mechanism. Appearance of the θ-rhythm in the hippocampus during the action of anticholinesterase and cholinomimetic substance apparently follows from changes in activity of the same system, with cholinergic mechanisms of the posterior hippocampus and septum probably playing a large role.
IT 357-70-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brain response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



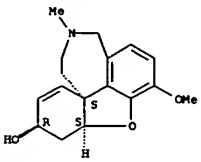
L11 ANSWER 254 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1968:94524 HCAPLUS
DOCUMENT NUMBER: 68:94524
TITLE: Presence of muscarine-sensitive neurons in the hippocampus
AUTHOR(S): Il'yuchenok, R. Yu.; Pastukhov, Yu. F.
CORPORATE SOURCE: Inst. Tsitol. Genet., Novosibirsk, USSR
SOURCE: Fiziologicheskii Zhurnal SSSR imeni I. M. Sechenova (1968), 54(2), 133-7
CODEN: FZLZAM; ISSN: 0015-329X
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB Expts. were made on cats (weight 2.3-3.3 kg.), the surgical operations (tracheotomy, scalping, insertion of a cannula into the femoral vein) were done under Et2O narcosis, cats were curarized with remyolan and were kept under artificial respiration; impulses from a single neuron of the hippocampus were measured by inserting micropipets filled with saline and connected to a cathode repeater and after amplification, recorded on a magnetic tape; activity of the motor and visual centers of the brain were recorded by inserting fine electrodes (30μ diameter). Prepns. tested were: galanthamine, eserine, arecoline, amisyl, benzacine, metacin, gangleron, and hexonium; all prepns. were injected i.v. at 3-0.2 mg./kg. Muscarinemimetic (arecoline) and anticholinesterase (galanthamine and eserine) substances increase the frequency of discharges in the main bulk of the hippocampal neurons. Muscarinolytics (amisyl and benzacine) decrease the frequency of discharges in the hippocampal neurons; changes in the activity of hippocampal neurons due to excitation and inhibition of muscarine-reactive structures indicate the presence of muscarine-sensitive (M-cholinergic) neurons in the hippocampus.

IT 357-70-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(brain response to)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



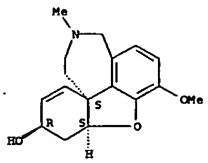
L11 ANSWER 255 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1968:67468 HCAPLUS
DOCUMENT NUMBER: 68:67468
TITLE: Ganglionic and central actions of galantamine
AUTHOR(S): Kostowski, Wojciech; Gumulka, Witold
CORPORATE SOURCE: Med. Acad., Warsaw, Pol.
SOURCE: International Journal of Neuropharmacology (1968), 7(1), 7-14
CODEN: IJNEAQ; ISSN: 0375-9458
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The actions of galantamine-HBr (I) on ganglionic transmission in the superior cervical ganglion of the cat and the spontaneous bioelec. activity of the brain were studied and compared with the activity of physostigmine salicylate (II). I injected intraarterially at 100-250 μg. prevented ganglionic blockade due to hexamethonium more strongly than comparable doses of II and increased the ganglionic depolarization induced by 10-20 μg. of acetylcholine chloride injected intraarterially. I caused periodic asynchronous postganglionic firing in the cat superior cervical ganglion. The mechanism of action of I resembles that of neostigmine rather than that of II and is not limited to the excitation of muscarinic cholinoceptive sites alone. I administered i.v. at 0.5-1.0 mg./kg. into unanesthetized cats caused a marked desynchronization of cortical and subcortical elec. activity, which was completely abolished by atropine sulfate or benactyzine-HCl administered i.v. at 0.3-0.4 and 1-2.5 mg./kg., resp.

IT 1953-04-4
RL: BIOL (Biological study)
(nervous system response to)

RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HBr

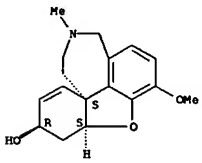
L11 ANSWER 256 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:515527 HCAPLUS
DOCUMENT NUMBER: 67:115527
TITLE: Effect of nivalin on the activity of aliesterases, acetyl and butyrylcholinesterase of rabbit spinal cord
AUTHOR(S): Venkov, L.; Eskenazi, M.; Mladenov, S.
CORPORATE SOURCE: Fac. Med., Sofia, Bulg.
SOURCE: Comptes Rendus de l'Academie Bulgare des Sciences (1967), 20(8), 863-5
CODEN: CRABAA
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rabbit spinal cord acetylcholinesterase and butyrylcholinesterase activities were inhibited in vitro by 98.4 and 99.5%, resp., by 10-4% nivalin. The inhibitory effect of nivalin was pronounced at a lower concentration (10-7%). Histochem. there was a simultaneous reduction of both cytoplasmic and membrane cholinesterase by nivalin; total inhibition of tissue acetylcholinesterase was achieved at 0.21%. Nivalin apparently inhibits some of the fractions of aliesterases; the A1 fraction of naphthylacetic esterase and A1 and A2 fractions of indoleacetic esterase were resistant to nivalin.

IT 1953-04-4
RL: BIOL (Biological study)
(cholinesterase inhibition by, in spinal cord)

RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HBr

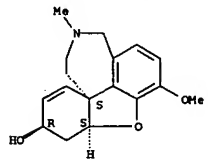
L11 ANSWER 257 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:431189 HCAPLUS
DOCUMENT NUMBER: 67:31189
TITLE: An attempt to differentiate so-called anticholinesterases into subgroups
AUTHOR(S): Prozorovskii, V. B.
CORPORATE SOURCE: Petrosavodsk. Gos. Univ., Petrosavodsk, USSR
SOURCE: Trudy Leningradskogo Pediatricheskogo Meditsinskogo Instituta (1967), No. 32, 126-31
CODEN: TLPMAP; ISSN: 0371-9324
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB The antagonism between some cholinopotentiators (anticholinesterases) and atropine in mice was studied and the effects of these anticholinesterases on frog rectus abdominis muscle were compared. Cholinopotentiators can be divided into 2 subgroups. Pyrophos, galanthamine, and pyroserine (active cholinopotentiators) make up one group and TEPP, eserine, and nibufin (weak cholinopotentiators) are in the second group. Cholinomimetic contraction was produced most by substances having the greatest potentiation on acetylcholine. Substances whose toxic action was only weakly inhibited by atropine had marked N-cholinopotentiating effects, while compds. strongly inhibited by atropine had a weak potentiating effect on acetylcholine. Consequently, pyrophos, mercaptophos, galanthamine, and proserine may be called predominantly N-cholinopotentiators and TEPP, eserine, armin, and nibufin predominantly M-cholinopotentiators. The middle member of the series, phosphacol, is presumably ambivalent. 34 references.

IT 357-70-0
RL: BIOL (Biological study)
(parasympatholytic activity of, atropine effect on)

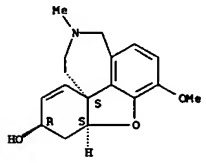
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 258 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:420246 HCAPLUS
DOCUMENT NUMBER: 67:20246
TITLE: Antagonism in the effects of different concentrations of anti- cholinesterases
AUTHOR(S): Dyablova, P. E.
CORPORATE SOURCE: Leningr. Pediatr. Med. Inst., Leningrad, USSR
SOURCE: Trudy Leningradskogo Pediatricheskogo Meditsinskogo Instituta (1965), No.ew, 34-8
CODEN: TLPMAP; ISSN: 0371-9324
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB On frog musculus rectus abdominis preparation low concns. of nivaline (I) [10-6 - 2 + 10-5] or mysuran (II) (2 + 10-7 - 2 + 10-5) evoked secondary contractions after 6-45 min. intervals. Concns. 5 + 10-5 and higher blocked contractile activity but after repeated washings with Ringer's solution the secondary reactions occurred. High concns. of I, II, or proserine blocked the secondary contractions evoked by the other compound Secondary contractions are explained by increased release of **acetylcholine** or by decrease of its enzymic hydrolysis, the block of contraction by accumulation of a pessimal concentration of **acetylcholine**. It is assumed that high concns. of anticholinesterase agents decrease the release of **acetylcholine**.
IT **1953-04-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(muscle response to)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

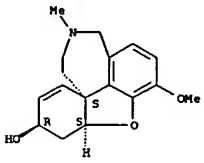
Absolute stereochemistry. Rotation (-).



● HBr

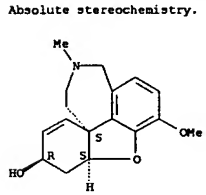
L11 ANSWER 259 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:64200 HCAPLUS
DOCUMENT NUMBER: 66:64200
TITLE: Administration of chemical substances to the central nervous system
AUTHOR(S): Kassil, G. N.
SOURCE: Sov. Probl. Fiziol. Patol. Nervn. Sist. (Moscow: Meditsina) (1965) 368-81
From: Ref. Zh., Biol., P. 1966, Abstr. No. 10P270
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB In expts. on rats, rabbits, cats, and dogs cholinergic prepns. (**acetylcholine** 5-50, carbocholine 1-50 γ, galanthamine 2-4 mg.) injected into the cerebrospinal fluid caused 3 phases of changes in electroencephalograms (EEG) and behavior, and autonomic changes: sympathetic (5-7 min. in cats), parasympathetic (10-15 min.), and sympathetic (30-40 min.). The effect of suboccipital injections was more intense than that of intraventricular injection. M-cholinolytic substances with a central action (diazyl, amizil, and atropine, i.v.) blocked activation of the sympathoadrenal system in response to cholinergic prepns. A cholinolytic substance with peripheral action (metacin 1-5 mg./kg. i.v.) had no influence on the effect of cholinergic prepns. Adrenolytics (aminazine 4-8 mg./kg., and ergotamine, i.v.) prevented behavioral and autonomic changes (but not changes in EEG). The effect of cholinergics is associated with their direct action on brain structures. Cholinergics activate 2 cholinergic links; near the ventricles (responsible for changes in behavior and EEG, and autonomic changes), and somewhat further removed from their lumens (responsible chiefly for changes in EEG). Sympathetic reactions were secondary and were associated with activation of adrenergic elements of the reticular formation of the brain stem.
IT **357-70-0**
RL: BIOL (Biological study)
(behavior and brain elec. activity response to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



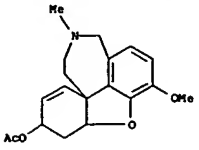
L11 ANSWER 260 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1967:27095 HCAPLUS
DOCUMENT NUMBER: 66:27095
TITLE: Role of adrenergic and cholinergic structures in the control of the pituitary-adrenal system
AUTHOR(S): Naumenko, E. V.
CORPORATE SOURCE: Inst. Cytol. and Genet., Novosibirsk, USSR
SOURCE: Endocrinology (1967), 80(1), 69-76
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Subcutaneous injections to guinea pigs of pipradrol, a drug having marked central effects but not exerting in usual doses a peripheral sympathomimetic effect, was not accompanied by stimulation of the hypothalamicpituitary-adrenal system. At the same time, amphetamine, producing central and peripheral sympathomimetric effects, and naphtyzin, stimulating mainly peripheral adrenoreactive structures, increased the corticosteroid level in peripheral blood of guinea pigs. A similar effect was produced by 2 anticholinesterases-galanthamin and neostigmine. Amphetamine, galanthamin, and neostigmine did not stimulate the hypothalamicpituitary-adrenal system in guinea pigs with midbrain sections. At the same time in these animals, activation of the brain cortex was observed by electroencephalography. In expts. in which anticholinesterases were used, besides electroencephalogram activation, a definite fall of acetylcholinesterase activity was noted at levels above the line of brain transection. Evidence is presented indicating that increased adrenocortical function after amphetamine, naphtyzin, galanthamin, or neostigmine administration is related to stimulation of peripheral adreno- and cholinoreactive structures. Epinephrine and **acetylcholine** may also exert their influence on the hypothalamic-pituitary-adrenal system by stimulating peripheral chemoreactive structures.
IT **357-70-0**
RL: BIOL (Biological study)
(adrenocortical function in response to, autonomic nervous system in relation to)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 261 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:432782 HCAPLUS
DOCUMENT NUMBER: 65:32782
ORIGINAL REFERENCE NO.: 65:6119c-g
TITLE: Some differences in the influence of anticholinesterase compounds on sensitivity of mice and rabbits to nicotine and arecoline
AUTHOR(S): Erkova, A. I.; Savateev, N. V.; Sofronov, G. A.; Sherstobitov, O. E.
CORPORATE SOURCE: S. M. Kirov Mil. Med. Acad., Leningrad
SOURCE: Doklady Akademii Nauk SSSR (1966), 167(5), 1197-200
CODEN: DANKAS; ISSN: 0002-3264
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB Subcutaneous injection of tetra-Et pyrophosphate (I), Armin, or galanthamine raised the sensitivity of mice to arecoline and nicotine, as determined by convulsion and tremor. The effect lasted for ≥ 1-2 hrs. A similar test with I and MeP(O)(OEt)SCH2CH2SEt.Me2SO4 (II) used in conjunction with nicotine and arecoline at selected dose levels showed that small doses of the anticholinesterase substances increased the action of arecoline on the heart for some 5 hrs. or even days. Both peripheral and central M-choline receptors were involved. In the case of nicotine, there was no significant difference between poisoning by anticholinesterase substances of short-term action or those with irreversible action. The results suggest that nicotine-like manifestations of intoxication by anticholinesterase substances depend mainly on direct action at the H-choline receptors, while the muscarine-like action results from inhibition of cholinesterase and stabilization of **acetylcholine** in the appropriate synapses. Animals poisoned by anticholinesterase substances and treated with reactivators (10-15 min. later) such as monoisonitrosoacetone and diacetyl monoxime, were then subjected to the action of nicotine or arecoline; animals poisoned by I recovered 60-95% of their brain cholinesterase activity from the above reactivators, which also prevented the convulsive reaction to nicotine and arecoline; TMB 4 (1,1'-trimethylenebis[4-formylpyridinium bromide)]reactivator similarly prevented the heart reaction to nicotine and arecoline after the administration of II, but in poisoning with Carbofos, this reactivator was effective only against nicotine, but not arecoline effects. Thus, anticholinesterase agents differ in the duration of enhanced reaction of the animal to nicotine and arecoline in central and peripheral choline-receptor regions. The parallelism between anticholinesterase action of organic P compds. and the reaction to arecoline suggested that at the M-choline receptors, potentiation of the effects of endogenous **acetylcholine** and M-cholinomimetic occurs; potentiation at H-choline-receptors is of shorter duration and is removed by the action of nucleophilic agents and without reactivation of cholinesterase. Possibly in this case, the cholinomimetic reacts more with the organic P compound than with **acetylcholine** itself.
IT **25650-83-3**, Galanthamine, acetate
(convulsions from arecoline and nicotine after administration of, effect of cholinesterase reactivators on)
RN 25650-83-3 HCAPLUS
CN Galanthamine, acetate (ester) (8CI, 9CI) (CA INDEX NAME)

L11 ANSWER 261 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 262 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1966:87307 HCAPLUS
DOCUMENT NUMBER: 64:87307
ORIGINAL REFERENCE NO.: 64:16463g-h,16464a
TITLE: Comparative investigation of the indirect stimulating action of a cholinesterase inhibitor
AUTHOR(S): Teitel, A.; Ghise, Doina
CORPORATE SOURCE: Pharm. Lab., Med. Pharm. Inst., Bucharest
SOURCE: Rev. Roumaine Physiol. (1965), 2(2), 115-21
DOCUMENT TYPE: Journal
LANGUAGE: German

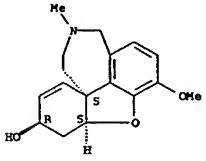
AB The isolated frog rectus muscle contracted sharply when diazinon, a cholinesterase inhibitor, was added to the bath after it had responded to added acetylcholine; the diazinon alone had no detectable effect. Most cholinesterase inhibitors have the same effect, and the degree of response depends on the concns. of acetylcholine employed and the duration of its contact with the muscle. The mechanism of action was assumed to be related to displacement of the acetylcholine, since curarelike drugs and membrane stabilizing agents blocked the response, while caffeine and hyaluronidase, agents increasing permeability, potentiated it.

IT 1953-04-4, Galanthamine, hydrobromide
(muscle response to, effect of acetyl-choline, caffeine and hyaluronidase on)

RN 1953-04-4 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HBr

L11 ANSWER 263 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1966:78588 HCAPLUS
DOCUMENT NUMBER: 64:78588
ORIGINAL REFERENCE NO.: 64:14772f-g
TITLE: The effect of galantamine on the blood pressure of the rat
AUTHOR(S): Chrusciel, M.; Varagic, V.
CORPORATE SOURCE: Med. Fac., Dept. Pharmacol., Belgrade, Yugoslavia
SOURCE: British Journal of Pharmacology and Chemotherapy (1966), 26(2), 295-301
CODEN: BJPCAL; ISSN: 0366-0826
DOCUMENT TYPE: Journal
LANGUAGE: English

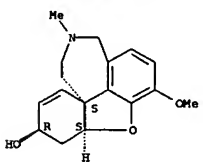
AB Galantamine (an alkaloid from Galanthus nivalis) produced a rise in blood pressure of the rat during urethan anesthesia. Tachyphylaxis towards the effect was also observed. Among the 6 anticholinesterases tested only the tertiary bases galantamine and physostigmine produced the hypertensive response. The quaternary substances had no effect. Hexamethonium and pentolinium did not block the hypertensive action of galantamine, whereas nicotine did. Adrenalectomy depressed the hypertensive action of galantamine only to a small extent. Atropine and adrenergic-blocking agents blocked it, whereas cocaine occasionally caused its potentiation. The effect of galantamine was absent in the pithed rat. No significant vasoconstrictor response to galantamine was seen in the perfused hind legs of the rat. The pressor response to galantamine is similar to the pressor effect of physostigmine and is due to a central stimulation of adrenergic nervous elements.

IT 1953-04-4, Galanthamine, hydrobromide
(blood pressure response to, effect of atropine, cocaine, etc., on)

RN 1953-04-4 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HBr

L11 ANSWER 264 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1966:70621 HCAPLUS
DOCUMENT NUMBER: 64:70621
ORIGINAL REFERENCE NO.: 64:13265b-e
TITLE: Role of the blood-brain barrier in neuro-endocrine-humoral regulation of functions
AUTHOR(S): Kassil, G. N.
SOURCE: Probl. Gisto-Gematich. Bar'erov (Moscow: Nauka) Sb. (1965) 105-12
From: Ref. Zh., Biol., P. 1965, Abstr. No. 24P7.
DOCUMENT TYPE: Journal
LANGUAGE: Russian

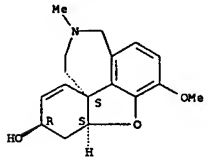
AB Results are given of expts. on the effect of cholinomimetic prepns.(acetylcholine (I), carbocholine (II), and galanthamine), injected intraventricularly and intraviscerally, on various body functions. Immediately after injection of I and II, sharp symptoms of excitation of various sections of the brain appeared. The sympathetic action phase, parasympathetic phase, and second sympathetic phase lasted 5-7, 10-15, and 30-40 min., resp., in cats. For intravisceral injection, the sympathetic effect was more pronounced. Intraventricular injection of I and II excited the reticular activating system and the posterior nuclei of the hypothalamus. Central M-cholinolytic prepns. (amysyl) and peripheral prepns. (Metacil) had the same effect 5-10 min. after intraventricular injection as an injection of amysyl into the blood. Central adrenolytic prepns. (aminazine) injected into the blood weakened the behavioral and vegetative reactions caused by intraventricular injection of I and II. Sympathetic reactions were associated with a secondary involvement of adrenergic synapses. When injected into the spinal fluid, the action of the prepns. was generalized in contrast to the natural path from the blood. Biol. active prepns. selectively penetrated through the blood-brain barrier into certain brain structures. The blood-brain barrier participated in neuro-endocrine-humoral regulation of functions of the entire organism.

IT 357-70-0, Galanthamine
(pharmacology of, hemato-encephalic barrier and)

RN 357-70-0 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



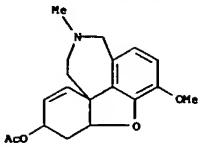
L11 ANSWER 265 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1966:13545 HCAPLUS
DOCUMENT NUMBER: 64:13545
ORIGINAL REFERENCE NO.: 64:2516g-h,2517a-c
TITLE: Participation of the acetylcholine -cholinesterase system in the mechanism of reticulocortical activation
AUTHOR(S): Il'yuchenok, R. Yu.; Nesterenko, L. N.
CORPORATE SOURCE: Inst. Cytol. and Genetics, Novosibirsk
SOURCE: Fiziol. Zh. SSSR (1965), 51(10), 1177-81
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB cf. CA 61, 8771h. The expts. were performed on 159 cats. There is a definite parallel between the degree of depression of acetylcholinesterase (I), the bioelec. activity of the brain, and the behavior of animals when various doses of anticholinesterase substances are administered. A clear-cut change in behavior ensues after the i.v. administration of galanthamine (II) in a dose of 3-5 mg./kg. A similar change in the general behavior takes place when eserine (III) is administered in doses approx. 10% as large as II, i.e., 0.2-0.3 mg./kg. When these doses of II and III are used which induce clear-cut behavioral reactions, a rapid low amplitude activity (16-24 oscillations/s.) is recorded on the EEG (EEG), which is characteristic of the waking-up reaction. A change in behavior and the presence of a pronounced cortical EEG activity are observed when I is depressed by II up to 8.8 ± 0.29% of normal in the cortex, up to 50.9 ± 5.5% in the thalamus, up to 33.9 ± 1.79% in the hypothalamus, up to 41.3 ± 8.6% in the mesencephalon, and up to 36.5 ± 3.1% in the medulla. A similar effect is observed when III is administered. The I activity in the blood is depressed to zero. When proserine (IV), a quaternary ammonium compound, is i.v. administered to cats in a dose of 0.1 mg./kg., the I of the blood is completely depressed, while the I of the brain is not substantially influenced. When IV (50-100 mg.) is introduced into the lateral ventricles of the brain, a pronounced depression of the I activity of the brain and a clear-cut EEG activating effect are observed The administration of large doses of II (5-10 mg./kg.) and III (0.5-1 mg./kg.) only slightly changes the degree of depression of I in the cerebral cortex, while the activating effect in relation to the EEG is increased. In the subcortical formations, the I activity is reduced proportionally to the dose of anticholinesterase substance administered, but remains rather high. In an isolated brain section, when a part of the mesencephalon still remains above the sectioning, II or III, along with depression of the activity, induced a clear-cut change in the bioelec. activity of the brain in the form of EEG activation. When the mesencephalon is completely sectioned off (premesencephalic section), EEG activation did not ensue. The presence of cortical activation may depend on the degree of depression of the I in the mesencephalic portion of the brain.

IT 25650-83-3, Galanthamine, acetate
(acetylcholinesterase and elec. activity of brain in response to)

RN 25650-83-3 HCAPLUS
CN Galanthamine, acetate (ester) (8CI, 9CI) (CA INDEX NAME)

L11 ANSWER 265 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

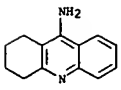


L11 ANSWER 266 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1965:457496 HCAPLUS
DOCUMENT NUMBER: 63:57496
ORIGINAL REFERENCE NO.: 63:10528e-f
TITLE: Some actions of tacrine on slow muscles of the toad (Bufo marinus) and the chick
AUTHOR(S): Porter, R. B.
CORPORATE SOURCE: Univ. Adelaide
SOURCE: British Journal of Pharmacology and Chemotherapy (1965), 25(1), 179-86
CODEN: BJPCAL; ISSN: 0366-0826
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of tacrine (I), neostigmine (II), tetraethylpyrophosphate (III), and physostigmine (IV) on the response of the toad rectus abdominus muscle to acetylcholine (V), carbachol, and decamethonium were investigated. I potentiated the response of the muscle to V to the same extent as II, slightly less than III, and approximately five-fold more than IV. The response to carbachol and decamethonium were unaffected by I. I potentiated the response of the rectus to V in the presence of IV (2.5 X 10-5M) but had no effect in the presence of higher concns. (10-4M), or after treatment with III. The responses of the semispinalis cervicis muscle of the chick resembled those of rectus except that I slightly depressed the response to decamethonium. The results indicate that the action of I in sensitizing slow contracting muscle to V is solely by inhibition of cholinesterase. Attention is drawn to the use of the I-treated muscle for the assay of V.

IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(in muscle response to acetylcholine, acetylcholine detection and)

RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



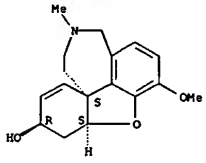
L11 ANSWER 267 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1965:85660 HCAPLUS
DOCUMENT NUMBER: 62:85660
ORIGINAL REFERENCE NO.: 62:15306e-g
TITLE: Pharmacologic actions of lycoramine
AUTHOR(S): Tang, Hsi-Kang; Chin, Kuo-Chang; Hsu, Pen
CORPORATE SOURCE: Acad. Sinica, Shanghai, Peop. Rep. China
SOURCE: Shengli Xuebao (1964), 27(4), 335-42
CODEN: SLHPAH; ISSN: 0371-0874
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB In anesthetized cats an intravenous injection of lycoramine at 3-5 mg./kg. produced a transient fall of systemic blood pressure, potentiated the hypotensive response elicited by acetylcholine or by the elec. stimulation of the peripheral end of vagus, and increased the activity of smooth muscle in the intestines. This drug also enhanced the blocking action of succinylcholine on the myoneural junction. Under the same exptl. conditions, galanthamine in doses of 0.25-2 mg./kg. produced similar effects. When the solution of lycoramine was applied locally to the rabbit eye, it caused pupillary constriction and abolished the mydriatic action of atropine. In vitro, lycoramine increased the reactivity of guinea pig ileum and frog rectus abdominis muscle to acetylcholine. In cats intravenous or intra-arterial (through lingual artery) injections of lycoramine or galanthamine produced no marked influence on the contractions of nictitating membranes elicited by elec. stimulation of preganglionic fibers, but they potentiated the action of acetylcholine injected through lingual artery. In EEG recordings of normal rabbits, lycoramine (15-20 mg./kg.) or galanthamine (3-5 mg./kg.) induced the arousal response and this action could be antagonized by some anticholinergic drugs such as atropine, scopolamine, or benactyzine.

IT 357-70-0, Galanthamine
(parasympathomimetic activity of, lycoramine and)

RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 268 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1965:62066 HCAPLUS
DOCUMENT NUMBER: 62:62066
ORIGINAL REFERENCE NO.: 62:11039h,11040a-c
TITLE: The effect of galanthamine and lycoramine on the choline-reactive system
AUTHOR(S): Chao, Kuo-Chu; Chao, Chiao-Ling; Hu, Chung-Chia
CORPORATE SOURCE: Dept. Pharmacol., Wuhan Med. Coll., Hankow, Peop. Rep. China
SOURCE: Yaoxue Xuebao (1965), 12(1), 36-44
CODEN: YHHPAL; ISSN: 0513-4870
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB When given intravenously, lycoramine (I) and galanthamine (II) caused in rabbits and cats a fall of blood pressure as well as an increase of the tonus and peristalsis of intestine. These responses could be antagonized by atropine. Solutions of I and II (both 0.5%) caused contraction of the pupil of rabbits to a variable extent. II (1 + 10-6 g./cc.) and I (1 + 10-5 g./cc.) produced contraction of isolated guinea pig ileum and still lower concns. of both increased the contraction induced by **acetylcholine**, BaCl2, and histamine. The effect of II on the muscle choline-reactive system was 5-10 times stronger than that of I. I and II increased the response caused by **acetylcholine** in the frog rectus and the leech dorsal muscle, the effect of II being slightly stronger than that of I. In cats and rats the two drugs caused an increase of contracting response of gastrocnemius muscle to nerve stimulation. The effect of I and II on the nerve-muscle prepns. was related to stimulating frequencies and doses. Higher frequencies (25-100/sec.) and larger doses caused, in many instances, depression of muscle contraction; lower frequencies (5-10/sec.) and smaller doses produced, in most instances, muscle contraction. The effect of II was 5 times stronger than that of I. After treatment with atropine the cholinesterase inhibitors, I and II, increased the depression of muscle contraction induced by **acetylcholine** in large doses. II, I, and neostigmine antagonized muscle paralysis induced by d-tubocurarine, but not by succinylcholine. Like neostigmine, I and II antagonized the ganglionic blockade produced by tetraethylammonium and also increased the contraction response of nictitating membrane to nerve stimulation. The stimulating effect of I on the central nervous system choline-reactive system was stronger than that of II. In mice, the L.D.50 values of I, II, and neostigmine were 0.958, 16.65, 0.174 mg./kg., resp.

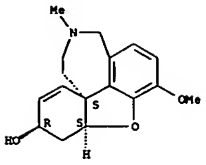
IT 357-70-0, Galanthamine
(parasympatholytic activity of)

RN 357-70-0 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 268 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L11 ANSWER 269 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1965:61952 HCAPLUS
DOCUMENT NUMBER: 62:61952
ORIGINAL REFERENCE NO.: 62:11019f-h,11020a
TITLE: Changes induced by galanthamine (nivalin) on the cardiovascular system
AUTHOR(S): Mortari, A.; Sioli, G.; Suppa, G.; Zocche, G. P.
CORPORATE SOURCE: Univ. Milan
SOURCE: Atti Accad. Med. Lombarda (1963), 18(3), 730-7
DOCUMENT TYPE: Journal
LANGUAGE: Italian

AB Galanthamine (I) hydrobromide was perfused into isolated rabbit hearts according to Langendorff at 25, 50, and 100 γ/l. Tyrode solution, and its action compared with that of 200 γ of Prostigmine (II)/l. I-induced electrocardiographic and arterial pressure changes were studied by giving I intravenously to guinea pigs (average weight 400 g.) at 2.5 and 5, and to rats (average weight 300 g.) at 1.25, 2.5, and 5 mg./kg. Pressor changes were studied also in animals pretreated with (drug, dose in mg./kg. intraperitoneally given) hexamethonium, 5; pentolinium, 5; chlorisondamine chloride, 1.5; dihydroergotamine (III), 2.5. Ten animals were cervical-6-spinalized 4 hrs. before I, and some of them treated intraperitoneally with 2.5 mg. of atropine (IV)/kg. I was also given to adrenalectomized animals (operated 72 hrs. prior to I). Addnl. animals were pretreated intraperitoneally with reserpine at 2.5, IV sulfate at 2.5 (4 hrs. and 30 min., resp., before I), iproniazid phosphate (V) at 100 mg. and 10 hrs. later with IV, or simultaneously with III and IV 30 min. before I. In animals pretreated with I (5 mg./kg. intraperitoneally) the electrocardiographic and pressor changes induced by intravenous **acetylcholine** (VI) (5, 10, and 50 γ/kg.) or epinephrine (VII) and norepinephrine (VIII) (2 γ/kg.) were studied. I had in vitro a VI-like action evidenced by a contractility decrease and an increase in coronary flow. The electrocardiographic changes were similar to those seen after II (500) or VI (50 γ/kg. intravenously). I displayed, on the cardiovascular system, a complex pattern of action with a predominance either of vagal (bradycardia, atrial and ventricular blockade, atrial extrasystole) or of sympathomimetic effects as hypertension (1.25 mg. of I/kg. gave a 50-60 mm. rise) which were unaffected by ganglion-blocking agents and V, and inhibited by parasympatholytic and hypotensive agents and in operated animals. VI-induced hypotension was potentiated by pretreatment with I, whereas no influence was observed on pressor responses to VII and VIII. It is suggested that the hypertensive effect is largely due to an increase of the vagal tone, owing both to a central stimulation of the orthosympathetic nervous system and to a release of catecholamines from the peripheral stores.

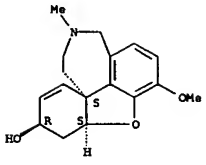
IT 1953-04-4, Galanthamine, hydrobromide
(circulatory response to)

RN 1953-04-4 HCAPLUS

CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

L11 ANSWER 269 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

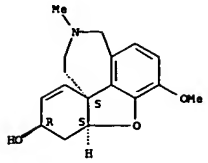


● HBr

L11 ANSWER 270 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1964:478991 HCAPLUS
DOCUMENT NUMBER: 61:78991
ORIGINAL REFERENCE NO.: 61:13783g-h,13784a-b
TITLE: Influence of pharmacological agents on choline reactive and adrenoreactive systems of the reticular formation and other regions of the brain
AUTHOR(S): Denisenko, P. P.
SOURCE: Proc. Intern. Pharmacol. Meeting, 1st, Stockholm, 1961 (1962), 8, 199-209
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. CA 57, 14387i. Chlorpromazine and methylbenactyzine depress the orientating reaction of mice. The biopotentials of the midbrain reticular formation and the cortex are changed more by antiarecoline drugs (benactyzine, methylbenactyzine) than by antinicotinic drugs (Trasentine, Parpanit). After elec. and cholinomimetic drug stimulation of the reticular formation, the antiarecoline drugs block the ascending activating system of the reticular formation in smaller doses than drugs of the antinicotinic group. On curarized cats acetylcholine produced a distinct stimulation of the cortex and reticular formation. Aprophen abolished this stimulation. A subsequent administration of acetylcholine in tenfold dose did not produce any stimulating effect. Nicotine caused greater changes in the electrocorticogram than in the activity of the reticular formation. This activity was abolished by benactyzine. After the administration of a central cholinolytic drug (methylbenactyzine), no activation reaction of the cortex by stimulation of the sympathetic nerve at the neck level was observed. Adrenaline changed the activity of the cortex and the reticular formation. Chlorpromazine abolished this stimulation. Repeated administration of adrenaline evoked no reaction. A subsequent administration of Nivalin produced an excitation. Nivalin produced a change of the electrocortigram and the activity of the reticular formation. Methylbenactyzine produced changes of opposite nature. Repeated Nivalin dose evoked no reaction. A subsequent amphetamine dose stimulated the reticular formation.
IT 1953-04-4, Galanthamine, hydrobromide
(effect on brain cortex and reticular formation)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

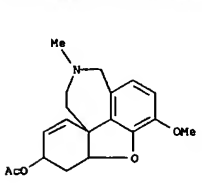
Absolute stereochemistry. Rotation (-).

L11 ANSWER 270 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



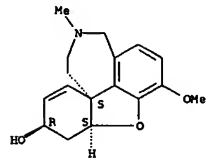
● HBr

L11 ANSWER 271 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1964:471692 HCAPLUS
DOCUMENT NUMBER: 61:71692
ORIGINAL REFERENCE NO.: 61:12492e-g
TITLE: Galanthamine, a new antidote of nondepolarizing muscular relaxants. Pharmacology and clinical use
AUTHOR(S): Slojanov, E. A.
CORPORATE SOURCE: Univ. Sofia, Bulg.
SOURCE: Anaesthesist (1964), 13(7), 217-20
CODEN: ANATAE; ISSN: 0003-2417
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB Galanthamine-HBr (Nivalin) (I-HBr) (m. 127-9°) has anticholinesterase activity. It potentiates acetylcholine and has no action on heart muscle, except in large dilns. of 10-3 when it shows an inotropic action resembling that of eserine. In investigations of the arterial blood pressure in cats. I-HBr in large doses had a biphasic action: an initial decrease followed by an increase in blood pressure of cats. Preinjection of atropine almost completely eliminated the hypotensive effect of small doses of I-HBr. I had direct action on skeletal musculature in cats. I-HBr had only slight toxicity in the mouse, rat, cat, and rabbit. Clin. I-HBr is an anticholinesterase, which shows a distinct antagonistic effect to nondepolarizing relaxants. A large therapeutic margin, good tolerance, and reliable action are the main advantages.
IT 25650-83-3, Galanthamine, acetate
(as antidote for muscle relaxants)
RN 25650-83-3 HCAPLUS
CN Galanthamine, acetate (ester) (8CI, 9CI) (CA INDEX NAME)



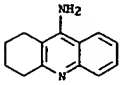
L11 ANSWER 272 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1964:93507 HCAPLUS
DOCUMENT NUMBER: 60:93507
ORIGINAL REFERENCE NO.: 60:16368g-h,16369a
TITLE: The comparative action of galanthamine hydrobromide and galanthamine methohydroxide on the nerve-muscle transmission
AUTHOR(S): Umarova, Sh. S.; Kamilov, I. K.; Polievtsev, N P.
SOURCE: Farmakol. Alkaloidov, Akad. Nauk Uz. SSR, Inst. Khim. Rast. Veshchestv (1962), (1), 184-9
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The influence of galanthamine-HBr (I) and galanthamine methohydroxide (II) on the in vivo contractions of gastrocnemius muscle induced by rectangular suprathreshold elec. impulses (0.5 per sec.) applied to the sciatic nerve was investigated in cats and rabbits in urethan narcosis. II in a dose of 0.1 mg./kg. intravenously increased the amplitude of gastrocnemius contractions by 100-250% for more than 15 min. At 0.5 mg./kg., II increases the contractions by 300%. Normally ineffective doses of acetylcholine (0.1-0.2 mg./kg.) after 0.1 mg./kg. of II caused an increase of gastrocnemius muscle contractions, and after 0.2 mg./kg. of II caused a decrease of contractions or complete, although transient, neuro-muscular block. II in a dose of 0.2 mg./kg. injected before delsemine, a curarelike substance (8 mg./kg.), counteracted its effect almost completely. II is 20-30 times more potent than I in the tests described.
IT 1953-04-4, Galanthamine, hydrobromide
(muscle-nerve transmission response to)
RN 1953-04-4 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

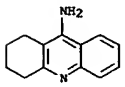


● HBr

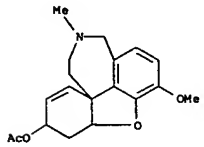
L11 ANSWER 273 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1964:41442 HCAPLUS
DOCUMENT NUMBER: 60:41442
ORIGINAL REFERENCE NO.: 60:7323c-d
TITLE: Some antagonists of atropine-like psychotomimetics
AUTHOR(S): Lang, W. J.; Gershon, S.; Holan, G.
CORPORATE SOURCE: Univ. Melbourne
SOURCE: Journal of Pharmacy and Pharmacology (1963), 15(12), 831-40
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The peripheral pharmacol. effects of ethylpiperidyl cyclopentylphenylglycolate (I) were similar to those of atropine. I inhibited parasympathetic effects and acetylcholine responses while pressor responses to adrenaline and noradrenaline were potentiated. Tetrahydroaminoacridine was shown to be an antagonist of I and a cholinesterase inhibitor. 2 and 3-Phenanthrylglycolic acids were antagonists to I, whereas phenoxymandelic acid was not.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(parasympatholytic activity of ethylpiperidyl cyclopentylphenylglycolate in relation to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



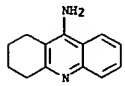
L11 ANSWER 274 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1963:450700 HCAPLUS
DOCUMENT NUMBER: 59:50700
ORIGINAL REFERENCE NO.: 59:9209b-d
TITLE: The actions of tacrine and amiphenazole on acetylcholine metabolism in the guinea pig ileum
AUTHOR(S): De la Lande, I. S.; Porter, R. B.
CORPORATE SOURCE: Univ. Adelaide
SOURCE: Australian J. Exp. Biol. Med. Sci (1963), 41, 149-62
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Tacrine (I) and amiphenazole (II) increase the excitability of the elec. stimulated ileum and restore excitability after depression by morphine (III). These effects are accompanied by inhibition of cholinesterase. Neither I nor II prevents the inhibitory action of III on acetylcholine (IV) release; thus the interaction of III and II or I on the elec. stimulated ileum is nonspecific, and in the case of I results from its effects on cholinesterase. The evidence that the excitatory action of II on the ileum is a consequence of its action on cholinesterase is less clear. II does not increase sensitivity to IV and instead depresses its output. Although I also depresses the output of IV, the effect is seen only in concns. approx. 1000-fold those producing equivalent inhibition of cholinesterase. Attention is drawn to the kinetics of inhibition of cholinesterase by I as a factor which may influence its physiol. actions
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(in acetylcholine metabolism by intestine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



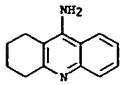
L11 ANSWER 275 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1963:424456 HCAPLUS
DOCUMENT NUMBER: 59:24456
ORIGINAL REFERENCE NO.: 59:4451a-b
TITLE: The mechanism of action of cholinergic substances after administration into the brain ventricles
AUTHOR(S): Kassil, G. N.; Latash, L. P.; Rutman, E. M.
SOURCE: Doklady Akademii Nauk SSSR (1963), 149(2), 464-7
CODEN: DANKAS; ISSN: 0002-3264
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Rabbits provided with a canula in the brain ventricles were subjected to the action of carbocholine and galanthamine with a recording of the elec. activity of the brain (typical waves shown). Carbocholine caused motor malfunctions in the animals and development of irregular high amplitude waves; galanthamine and, to a lesser degree acetylcholine, produced similar effects. Atropine blocked the elec. activation either preor postadministratively. Aminazine immediately removed the central effects of acetylcholine, carbocholine, or galanthamine. Evidently the reticular activating system contains a cholinergic link.
IT 25650-83-3, Galanthamine, acetate
(brain elec. activity response to)
RN 25650-83-3 HCAPLUS
CN Galanthamine, acetate (ester) (8CI, 9CI) (CA INDEX NAME)



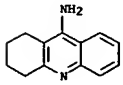
L11 ANSWER 276 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1963:42437 HCAPLUS
DOCUMENT NUMBER: 58:42437
ORIGINAL REFERENCE NO.: 58:7279d-e
TITLE: Potentiating action of Tacrine on the effects of succinylcholine
AUTHOR(S): Huegin, W.
CORPORATE SOURCE: Univ. Basel, Switz.
SOURCE: Anaesthesist (1962), 11, 338-40
CODEN: ANATAE; ISSN: 0003-2417
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The anticholinesterase drug Tacrine (1,2,3,4-tetrahydro-5-aminoacridine) (I), which is characterized by high anti-cholinesterase activity, low muscarinic action, and a cerebral analeptic effect, was used in 50 patients to prolong the action of succinylcholine (II). I, when given in a dose of 0.5 mg./kg. prior to the 1st injection of II, prolonged the action of II up to 15 min. Doses of 0.3-0.4 mg./kg. II were then supplied as frequently as necessary (about every 15 min.) to maintain relaxation.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(in muscle response to acetylcholine, in muscle response to succinylcholine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 277 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1962:437450 HCAPLUS
DOCUMENT NUMBER: 57:37450
ORIGINAL REFERENCE NO.: 57:7543d-f
TITLE: Estimation and urinary excretion of tetrahydroamino acridine
AUTHOR(S): Kaul, P. N.
CORPORATE SOURCE: Univ. Melbourne
SOURCE: Journal of Pharmacy and Pharmacology (1962), 14, 237-42
CODEN: JPPMAB; ISSN: 0022-3573
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Two methods for the quant. determination of tetrahydroaminoacridine (I) in aqueous solns. and in urine in the range, 0.2-3.0 γ/ml. are described. One is based on the colorimetric estimation at 508 mμ of the colors formed with methyl orange and I; the second is based on the spectrophotometric estimation of I at 323 mμ, the absorbance ratio at 323: 335 mμ may be used to characterize I. Four metabolites were isolated from rat urine. Two of these, constituting the major proportion of the total metabolites, were also isolated from human urine and were partially characterized by paper chromatography.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro- (determination in urine)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 278 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1962:76402 HCAPLUS
DOCUMENT NUMBER: 56:76402
ORIGINAL REFERENCE NO.: 56:14869a-c
TITLE: The action of hydroaminacrine and some other acridine compounds on isolated guinea pig ileum
AUTHOR(S): Jensen-Holm, J.; Teglbjerg, K. Stubbe; Hougs, W.
CORPORATE SOURCE: Univ. Copenhagen
SOURCE: Acta Pharmacologica et Toxicologica (1961), 18, 370-8
CODEN: APTOA6; ISSN: 0001-6683
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Hydroaminacrine (1,2,3,4-tetrahydro-9-aminoacridine chloride) (I) in glucose-containing fluid in doses below 1 γ/25 ml. gave only slight contractions of the intestine; in doses of 1 to 10 γ, contractions increased with dosage. The maximum effect was at doses of 1-4 γ. I in glucose-free fluid with concns. of 1-10 γ did not result in any contractions. Pretreatment with atropine (1-5 γ) for a few min. followed by I, prevented shortening of the intestine. Pretreatment with mepyramine (5 γ) did not prevent contraction by I. In the presence of acetylcholine, I gave a synergistic action; the same action occurred in the presence of neostigmine. Acridine (10-30 γ) produced no contraction; 9-aminoacridine (10 γ) produced moderate contraction. Euflavine (10-80 γ) and mepacrine (10-30 γ) produced little or no contraction. I intensified the relaxation effect of (+)-tubocurarine and the contraction effects of gallamonium, decamethonium, and suxamethonium.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro- (intestine response to)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

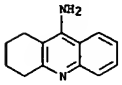


L11 ANSWER 279 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1962:13213 HCAPLUS
DOCUMENT NUMBER: 56:13213
ORIGINAL REFERENCE NO.: 56:2515a-c
TITLE: Galanthamine, powerful natural cholinergic. I. Sources, chemical structure, characterization, extraction, toxicity, and action on smooth fibers
AUTHOR(S): Boissier, Jacques R.; Combes, Georges; Pagny, Jeannette
CORPORATE SOURCE: Fac. Med., Paris
SOURCE: Ann. Pharm. Franc. (1960), 18, 888-900
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Galanthamine (I), found chiefly in the Galanthus woronowii, forms colorless crystals, m. 128-9°, slightly soluble in H2O and ether, soluble in most of the usual organic solvents; hydrobromide, m. 234-5°; [α]20D = - 93° ± 2 (c, 2% in H2O); ultraviolet maximum in H2O, 288 mμ (E1%1cm. = 68); infrared (KBr) absorption bands are: 3370; 2910; 1953; 1625; 1505; 1435; 1382 cm.-1 I gives characteristic alkaloidal reactions with Meyer and Dragendorff reagents, and with silicotungstic acid. The ratio of toxicity of I as compared to neostigmine (II), (L. D.50 I/L. D.50 II) is 16.5 intravenously, and 21.3 intraperitoneally; atropine diminished toxicity. I increased the strength of the contraction of the isolated ileum of the guinea pig treated with acetylcholine. The essential action of I is its power to increase the activity of acetylcholine, the mechanism being related to an anticholinesterase effect. 26 references.
IT 25650-83-3, Galanthamine, acetate (chemistry and pharmacology of)
RN 25650-83-3 HCAPLUS
CN Galanthamine, acetate (ester) (8CI, 9CI) (CA INDEX NAME)

L11 ANSWER 280 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1961:132861 HCAPLUS
DOCUMENT NUMBER: 55:132861
ORIGINAL REFERENCE NO.: 55:25053b-c
TITLE: Some toxicologic properties of the alkaloids galanthamine and securinine
AUTHOR(S): Friess, S. L.; Durant, R. C.; Whitcomb, E. R.; Reber, L. J.; Thommesen, W. C.
CORPORATE SOURCE: Natl. Naval Med. Center, Bethesda, MD
SOURCE: Toxicology and Applied Pharmacology (1961), 3, 347-57
CODEN: TXAPA9; ISSN: 0041-008X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. ibid. 2, 574-88. Galanthamine (I) was approx. 3 times more effective than securinine (II) as an in vitro inhibitor of the acetylcholinesterase-acetylcholine system. The enzyme-inhibitor dissociation constants at pH 7.4 and 25.14° in dilute phosphate buffer were (1.2 ± 0.1) + 10-7 and (1.6 ± 0.1) + 10-4 for I and II, resp. The intravenous L.D.50 values of I and of II in mice were 5.2 ± 0.2 and 3.5 ± 0.9 mg./kg., resp. In its effects on the node of Ranvier from Rana pipiens sciatic nerve and its toxicity syndrome in mice and cats, I proved very similar to physostigmine. II was a very powerful convulsant and paralyzant in mice and cats, with actions similar to those of strychnine, and a weak nodal blocking agent.
IT 357-70-0, Galanthamine (acetylcholinesterase inhibition and toxicity of)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

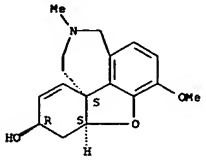
Absolute stereochemistry. Rotation (-).

L11 ANSWER 281 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1960:120372 HCAPLUS
DOCUMENT NUMBER: 54:120372
ORIGINAL REFERENCE NO.: 54:23047f-g
TITLE: Blocking effect of tetrahydroaminacrine on a new psychotomimetic agent
AUTHOR(S): Gershon, Samuel
CORPORATE SOURCE: Univ. of Michigan, Ypsilanti
SOURCE: Nature (London, United Kingdom) (1960), 186, 1072-3
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB N-Ethyl-3-piperidyl 2-cyclopentyl-2-phenylglycolate (I) induces in mice a model psychosis and the central and peripheral effects of an acetylcholine inhibitor. Tetrahydroaminacrine, 1,2,3,4-tetrahydro-5-aminoacridine (II), a cholinesterase inhibitor, completely abolishes all psychotomimetic symptoms of I. Eight human subjects given 10-20 mg. of I intramuscularly showed varied psychomimetic symptoms 20 min. after drug administration. Intravenous injection of 30-60 mg. II completely abolished the induced state of I within 2 min.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(antagonism to psychotomimetic action of 1-ethyl-3-piperidinol α-cyclopentylmandelate)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)

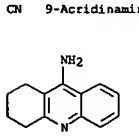


L11 ANSWER 282 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1956:50027 HCAPLUS
DOCUMENT NUMBER: 50:50027
ORIGINAL REFERENCE NO.: 50:9626c-e
TITLE: Effects of galanthamine on the acetylcholine sensitivity of skeletal musculature
SOURCE: M. D. Mashkovskii. Farmakol. i Toksikol. (1955), 18(No. 4), 21-7
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB Galanthamine differs greatly in chemical structure from other anticurare drugs; its formula is I. It sensitizes skeletal muscles to AcOCH2CH2NMe3OH and is antagonistic to tubocurarine and diplacin, restoring the neuromuscular conduction which they inhibit. It enhances the curarizing action of AcOCH2CH2NMe3OAc. Its use is indicated in neuromuscular impairment.
IT 357-70-0, Galanthamine
(effect on muscles sensitivity to acetylcholine)
RN 357-70-0 HCAPLUS
CN 6H-Benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6R,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 283 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1956:21257 HCAPLUS
DOCUMENT NUMBER: 50:21257
ORIGINAL REFERENCE NO.: 50:4383f-h
TITLE: Action of morphine and antagonists of the narcotic action of morphine on acetylcholine synthesis in brain
AUTHOR(S): De la Lande, I. S.; Bentley, G. A.
CORPORATE SOURCE: Univ. Melbourne
SOURCE: Australian Journal of Experimental Biology and Medical Science (1955), 33, 555-66
CODEN: AJEBAK; ISSN: 0004-945X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C.A. 50, 479e. Morphine (I), the morphine antagonists 2,4-diamino-5-phenylthiazole (II), 1,2,3,4-tetrahydro-5-aminoacridine (III), 5-aminoacridine (IV), and eserine (V), and proflavine (VI) (a pharmacologically inactive acridine derivative) inhibit the acetylation of choline in whole cell prepns. of rat brain, but none inhibits acetylation of choline by cell-free exts. of rat brain. The inhibition by I of choline acetylation by whole cell prepns. is reversible but inhibition by II is only partly so. The inhibitory effects of I and II are additive. Inhibition by VI occurs at concns. which also cause protein precipitation
III,
but not I or II, inhibits acetylation of aminoazobenzene by aged pigeon-liver extract; the concentration required will also cause protein precipitation
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(effect on acetylcholine formation in brain)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L11 ANSWER 284 OF 284 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1954:73473 HCAPLUS
DOCUMENT NUMBER: 48:73473
ORIGINAL REFERENCE NO.: 48:13055c-e
TITLE: The pharmacology of some new anticholinesterases
AUTHOR(S): Shaw, F. H.; Bentley, G. A.
CORPORATE SOURCE: Univ. Melbourne
SOURCE: Australian Journal of Experimental Biology and Medical Science (1953), 31, 573-6
CODEN: AJEBAK; ISSN: 0004-945X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Anticholinesterase activity of specific acridines, pyrimidines, and thiazole derivs. were measured. Compds. found to have anticholinesterase activity were: 2-aminoacridine (I), 3-aminoacridine (II), 4-aminoacridine (III), 5-aminoacridine, 1-methyl-5-aminoacridine, and 1,2,3,4-tetrahydro-5-aminoacridine. Atropine-like effects were observed in I, 1-methyl-5-aminoacridine (IV), 2,8-diaminoacridine (V), 1,2,3,4-tetrahydro-5-aminoacridine (VI), 2-aminopyridine, 4-aminopyridine (VII), and 2,4-diamino-5-phenylthiazole. The following compds. exhibited the specific effects listed: 1-aminoacridine and 5-aminoacridine potentiate the action of acetylcholine (ACh) in uterus and gut. I, III, V, and 1,9-dimethyl-2,8-diaminoacridine potentiate only the uterine musculature, for ACh. II exerts its effects upon the gut and rectus musculature only. VII has its specific activity on the gut only. IV potentiates the musculature of the uterine and rectus muscles to ACh. VI exerts moderate effects upon the gut, rectus, and uterine muscles.
IT 321-64-2, Acridine, 9-amino-1,2,3,4-tetrahydro-
(anticholinesterase activity of)
RN 321-64-2 HCAPLUS
CN 9-Acridinamine, 1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)